FREELY AVAILABLE PROSTATE SPECIFIC ANTIGEN TESTING IN A POPULATION: TESTING PATTERNS AND OUTCOMES ON PROSTATE CANCER *THE SASKATCHEWAN EXPERIENCE*

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ABSTRACT

Background: The prostate specific antigen (PSA) test has been available for physicians and free of charge to residents in Saskatchewan since 1990. The PSA test witnessed great growth in use indicative of screening but it was unknown who was being tested, how often, which physicians were ordering PSA tests, or what the variation in utilization was in the population. Whether widespread use of the PSA test resulted in a stage shift among newly diagnosed prostate cancers or changed the clinical management of the disease was also unknown. The purpose of this research was to describe in detail how the PSA test is being used in the Saskatchewan population and investigate the impact of testing on the diagnosis and clinical management of prostate cancer during the PSA era.

Methods: Individual records were retrieved from the two labs in Saskatchewan capable of analyzing PSA serum samples. The PSA data represented almost all PSA tests in the population for the five-year period 1997-2001. The PSA data included date of the PSA test, a unique identifier of the men tested, test results including total PSA and the free-PSA amount (for November 1999 to December 2001), and an ID of the physician who ordered the test. This data was linked to the population-based Saskatchewan Cancer Registry to determine who had a previous or subsequent prostate cancer diagnosis and to secure tumour characteristics and clinical management data. This combined data was then linked to Saskatchewan Health data files to obtain information about biopsy procedures and to determine the geographic residence of men at the time of their PSA tests. De-identified data was returned for descriptive analysis.

Results: Over 60% of men aged 50 and over had at least one PSA test during 1997 to 2001. Even among men 40-49, 27% had at least one PSA test and there were over 5,300 tests done in men under 40 years of age. Sixteen percent of men 40-49 who had PSA tests had more than one and this percentage increased with age to 59.4% for men in their 70's. Over 80% of all PSA tests were ordered by general practitioners and

there were significant geographic variations in testing patterns. Knowledge of the free-PSA-ratio, which began in 1999, reduced biopsy rates 4.7% and increased cancer detection 8.7% for men with total PSA test results in the 4.0-10.0ng/ml range, however these rates were also very age specific. The age-adjusted incidence rate of organ confined disease increased from 38.5 per 100,000 to 108.8 per 100,000 from 1985 to 2001. Almost 80% of prostate cancers were detected by needle biopsy in 2001 compared to only 34% in 1985, while 20% of cases in 2001 were treated with radical surgery compared to only 2% for 1985. Mortality rates have remained stable up to 2001.

Conclusion: PSA testing is very common in Saskatchewan consistent with extensive screening activity. Conflicting guidelines and the universal availability of the test has resulted in significant inappropriate testing and considerable variation of use. Most prostate cancers are now found by needle biopsy and are organ confined at the time of diagnosis. No benefit in prostate cancer mortality has yet been realized in Saskatchewan from extensive PSA testing.

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GLOSSARY OF TERMS

Invasive: Cancer that has spread beyond the tissue of origin and is growing into surrounding healthy tissues.

Incidence: The number of new cases of a disease diagnosed each year

Mortality: For the purposes of this research, primary cause of death reported on death certificates.

Prevalence: the number of events (for this research, men in the population with known prostate cancer) at a point in time.

Metastasis: The spread of cancer from one part of the body to another. The metastatic tumor contains cells that are like those in the original tumor.

Local disease (cancer): The spread of cancer from the site or origin to nearby tissues.

Stage: The extent of a cancer in the body. Stage at time of diagnosis is usually based on the size of the tumor at diagnosis, whether the cancer has spread from the original site to or to other parts of the body.

Grade: The grade of a tumor is a measure of the abnormality of the cancer cells as viewed under a microscope and reflects how quickly the tumor is likely to grow and spread. Grading systems are different for each type of cancer.

Gleason Score: A system of grading prostate cancer tissue based on how it looks under a microscope. Gleason scores range from 2 to 10 and indicate how likely it is that a tumor will spread. A low Gleason score means the cancer tissue is similar to normal prostate tissue and the tumor is less likely to spread; a high Gleason score means the cancer tissue is very different from normal and the tumor is more likely to spread.

1.0 INTRODUCTION AND BACKGROUND

Prostate specific antigen (PSA) is a glycoprotein produced by prostatic epithelial cells. Elevated levels of PSA in blood serum are associated with prostate enlargement and indicate increased risk of prostate cancer. The PSA test was developed to measure the level of PSA in serum and initially was used as a follow-up test for men with prostate cancer. However, because of the association of elevated PSA with increased risk of cancer, the test over time is now commonly used as a screening tool for the early detection of prostate cancer. Two large screening trials were initiated, one in the United States and the other in Europe, to investigate whether screening for prostate cancer with PSA provides any mortality benefit from prostate cancer but thus far, neither have provided definitive results.[1, 2]

In Saskatchewan, the PSA test became available for physicians to use for their patients in 1990 and the test was covered by the provincial health plan, making it free of charge to the patient. This created a rather unique situation, where all residents had access to the PSA test at no cost. The use of the PSA test grew dramatically and during the time period after its introduction, prostate cancer rates in Saskatchewan rose substantially.[3]

This thesis work will take advantage of existing population-based databases to investigate PSA test use and outcomes associated with this testing activity in Saskatchewan, which has never been reported. Three projects are contained in this thesis and each project is provided as a separate chapter in the style of a manuscript. The projects, collectively, explore how the PSA test has been used in Saskatchewan; what physician groups order the PSA test and who is being tested; what variations are there in the population of men being tested in terms of geography, frequency of testing, age distribution; what are the test results and how do they distribute in the population of men tested? As well, this thesis work will provide a description of the outcomes of PSA testing in the Saskatchewan population, in terms of changes in cancer detection, tumour characteristics of newly diagnosed prostate cancers, and clinical management.

Many of these questions remain unanswered in jurisdictions where PSA testing is commonly used. This work will provide important information about widespread PSA testing in a population where the test is freely available but where screening is not actually fully endorsed. It is unknown whether our testing patterns reflect any of the screening guidelines that exist from organizations that have put forward recommendations on the early detection of prostate cancer.

This Introduction and Background section is followed by a brief description of the research and then by a literature review on the subject of PSA testing and the key issues associated with prostate cancer screening. After the literature review are three chapters, each one a specific project investigating the elements of the issues mentioned above. Finally a Discussion and Conclusion section will summarize the findings of this research and provide recommendations about potential next steps in the Saskatchewan context.

1.1 Prostate Cancer: Burden of Disease in Saskatchewan

The prostate is a chestnut shaped gland found at the beginning of the urethra in males. One of its main functions is the production and secretion of fluid that makes up about a third of the volume of semen that a male ejaculates. The prostate is also a common site of cancer in men. The risk of disease increases with increasing age. The following section describes the burden of disease of prostate cancer in Saskatchewan in terms of incidence, mortality, years of life lost, and trends over time.

Prostate cancer is the most common invasive cancer diagnosed in Saskatchewan males. Among 2,429 new cases of invasive cancer diagnosed in men in 2002, 771 cases, or almost exactly one in three were prostate cancer.[4] Overall, prostate cancer represents about 17% of all new invasive cases per year in the Saskatchewan population including females. The burden of this disease has increased over time, in part, because of its strong association with increasing age, and the ageing of the Saskatchewan population.[4, 5]

Figure 1.1 shows the age-specific incidence rates for prostate cancer in Saskatchewan in 2002. After age 50, incidence increases dramatically. There are now also many more men in Saskatchewan over age 50 than ever before. In 1970, there were 112,562 men age 50 or older and by 2002, this number was 140,692, an increase of 25 percent.[5] Given the aging population of Saskatchewan, the burden of prostate cancer is expected to increase in the foreseeable future.

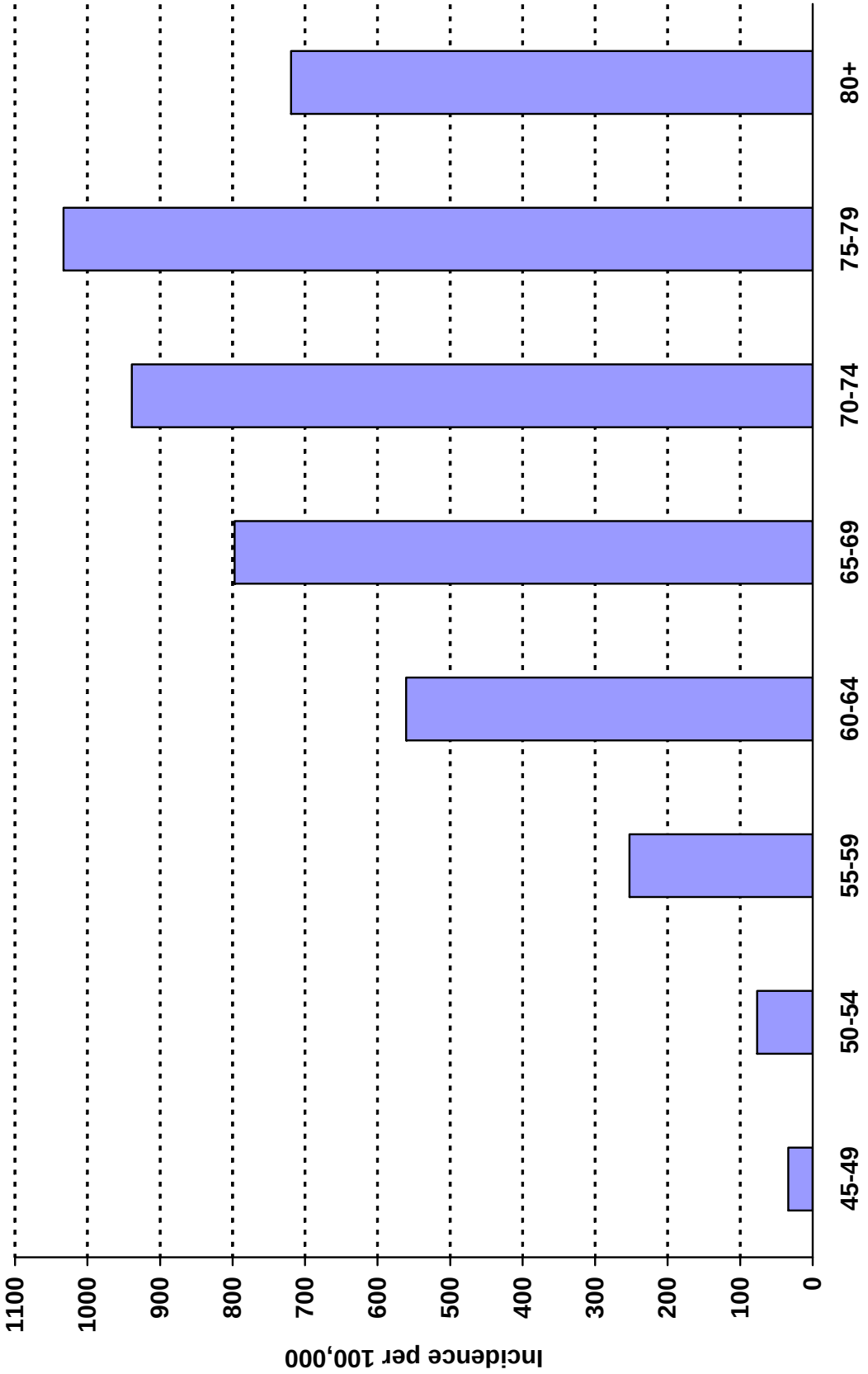

Figure 1.1 Age-Specific Incidence of Prostate Cancer in Saskatchewan, 2002

The distribution of the most common cancers in Saskatchewan men has changed over time (Figure 1.2).[5] In the 1950-1954, prostate cancer was the most common invasive cancer representing 15% of cases, but cancers of the lip and stomach were very close in terms of absolute numbers. In 1997-2001, prostate cancer was twice as common as lung cancer, the second leading site, and accounted for 30% of all invasive cases diagnosed in males.

Incidence and mortality trends for prostate cancer show different patterns in Saskatchewan and between Saskatchewan and Canada overall. The age-adjusted incidence rate in Saskatchewan showed marked increase beginning in 1990, coinciding with the introduction of the PSA test (Figure 1.3).[4, 6] A peak in incidence was reached in 1993 followed by a drop to previous levels. A similar pattern occurred in Canada, however the peak was not as great as was experienced in Saskatchewan. Following a three-year period of stability, the incidence in Saskatchewan again began to increase quickly and by 2001 had again reached peak levels previously seen in 1993. In Canada, the "wave" began at the same time but again was less steep and did not reach the same peak as witnessed in Saskatchewan. Similar patterns had been observed in other jurisdictions, with the magnitude of change likely related to the amount of PSA testing in those areas.[7]

The sharp increase in incidence rates (50% from 1990 to 1994) followed by the return to previous trends is very indicative of a screening effect in the population.[8] In the presence of (new) screening activities, the number of new cases diagnosed of the target disease usually increases because the activity identifies more of the prevalent cases (the number of cases in existence in the population at a given point in time) in the population, which would not have been identified in the absence of screening. After some time, the incidence returns to previous levels and trends, once the prevalent cases have been identified and most of the target population has been tested.[8]

Although incidence has changed significantly over time, the trend in prostate cancer mortality has been almost constant (Figure 1.3). There had been little difference in mortality rates between Saskatchewan and Canada from 1983 to 1994. Since 1994 though, mortality rates in Canada have decreased whereas they remained stable in

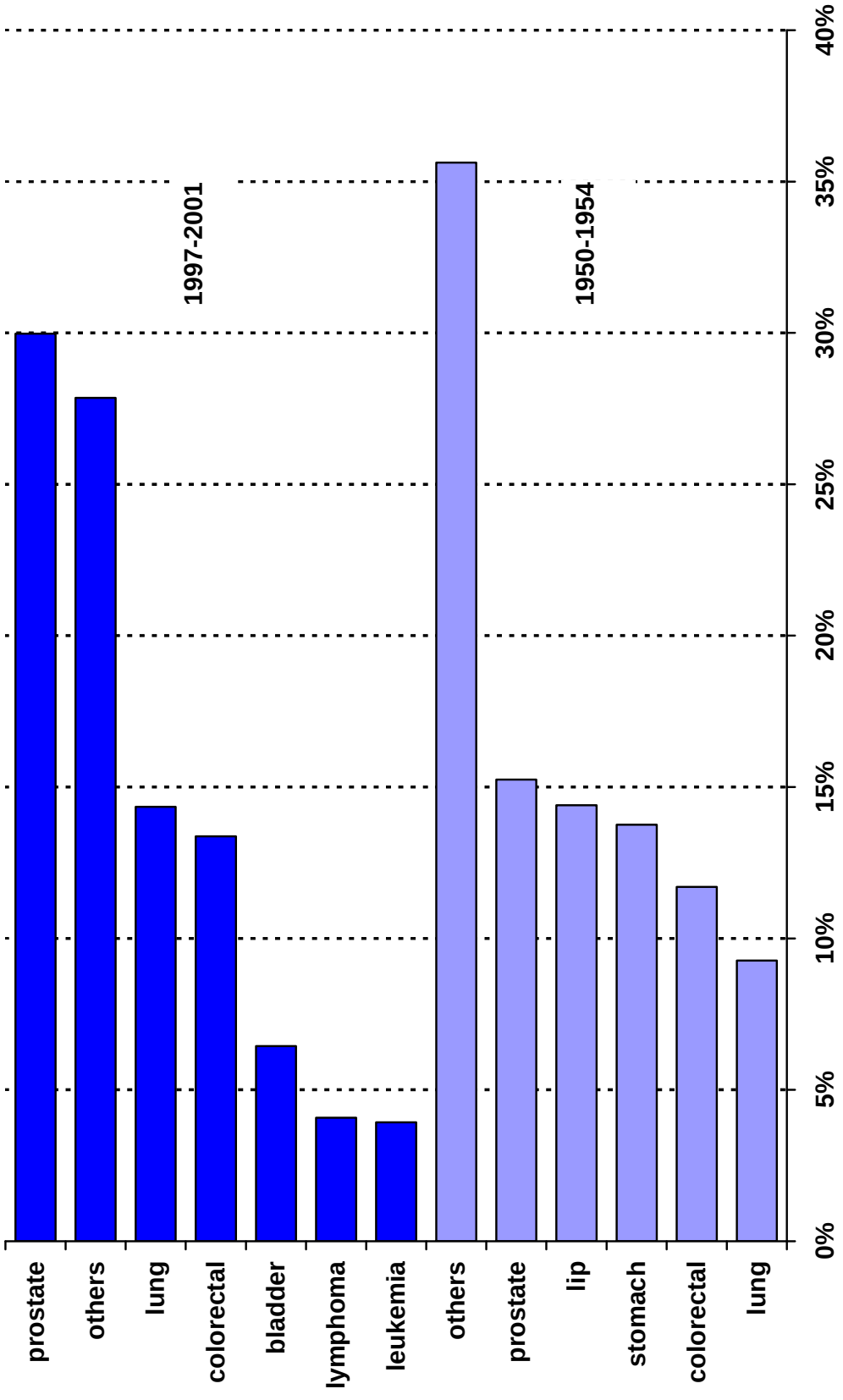

Figure 1.2 Percent of Invasive Cancers Diagnosed in Males, 1950-1954 and 1997-2001

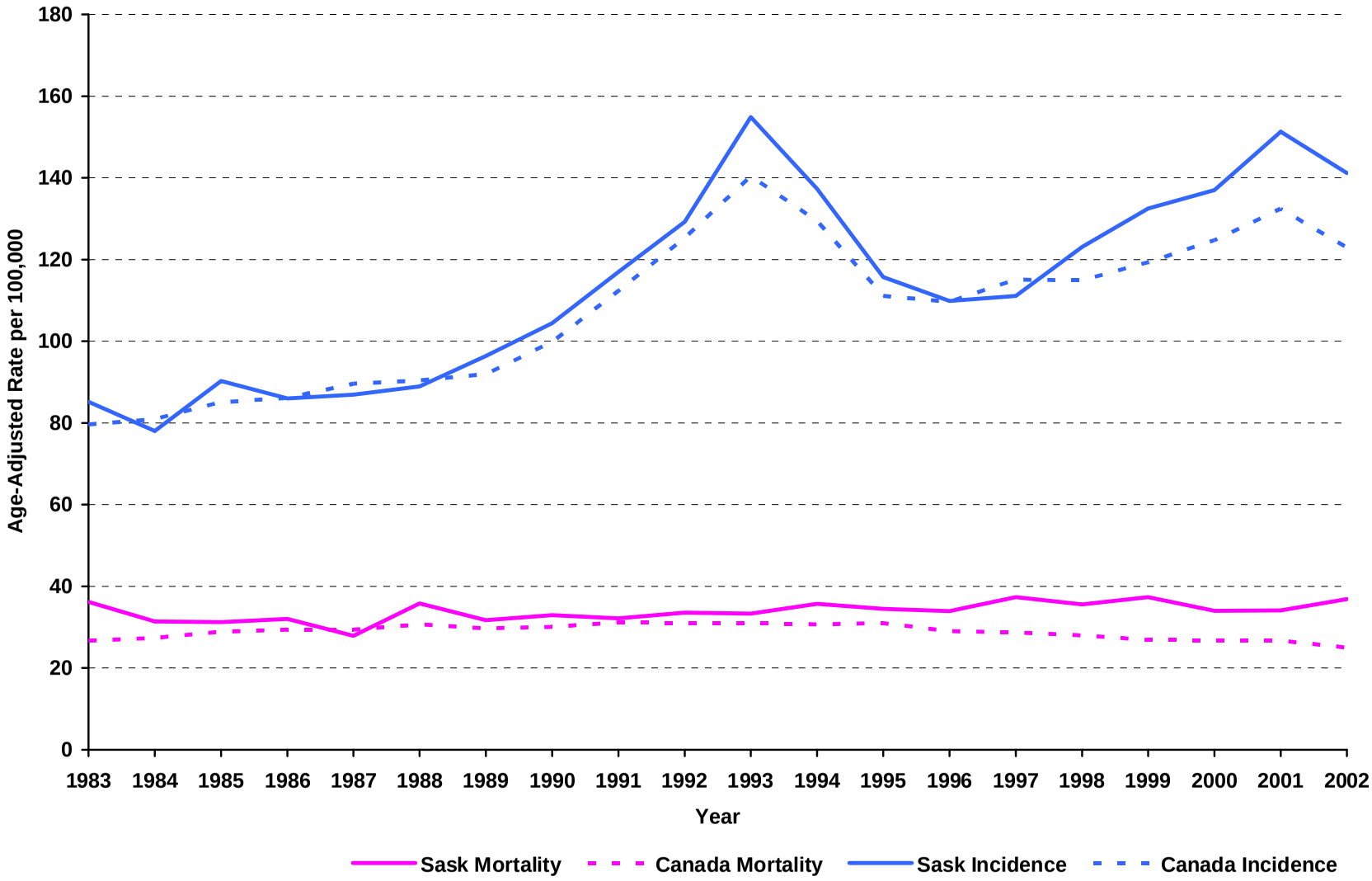

Figure 1.3 Age-Adjusted Incidence and Mortality Rates of Prostate Cancer

Saskatchewan. Decreases in prostate cancer mortality might result from the screening activity of the 1990's if cancer was diagnosed at earlier stages with better prognosis. But mortality improvements would not be realized for years given the overall five-year relative survival is about 82%.[3, 9] As well, the lead time (time gained by detecting cancer earlier than usual because of screening) associated with PSA screening has been estimated to be between 5 and 9 years, therefore if mortality decreases at all, this would likely not be realized until sometime in the mid 2000's.[10] Whether *any* benefit of prostate cancer screening is possible is currently a highly contested issue.[11, 12]

Potential-years-of-life-lost (PYLL) is another measure of disease burden. PYLL measures the loss in a society due to early death. The calculation of PYLL was based on provincial life tables published by Statistics Canada.[13] The annually published life tables indicate for each sex in Saskatchewan, the life expectancy in years for each single year of age (e.g. 50, 51, 52). People who died of cancer were matched to the life tables based on age (single year) at time of death, sex, and year. The total and average PYLL due to various cancer sites for men in Saskatchewan are shown in Figure 1.4. The total PYLL from prostate cancer for the period 1997-2001 was second only to lung cancer for men. For this period, there was 9,585 PYLL due to prostate cancer. On average however, PYLL due to prostate cancer is significantly less than many other cancer sites. The total PYLL is high because there are many deaths attributed to prostate cancer, but the average PYLL per person is lower because deaths are generally in much older men, who typically would not expect to live many more years, compared to deaths in men that are caused by other cancers.

1.2 Prostate Specific Antigen Test: Background in Saskatchewan

Prostate cancer witnessed continued growth in incidence over the past fifty years, but none larger than in the 1990s, a time coinciding with the introduction of the serum prostate specific antigen (PSA) test in 1990. The PSA test was initially used in other jurisdictions in the 1980s as a follow-up test to investigate disease recurrence and progression for men with prostate cancer. This important use remains today but the utility of the test expanded in the late 1980s and 1990s to include early diagnosis and screening, albeit under much controversy.

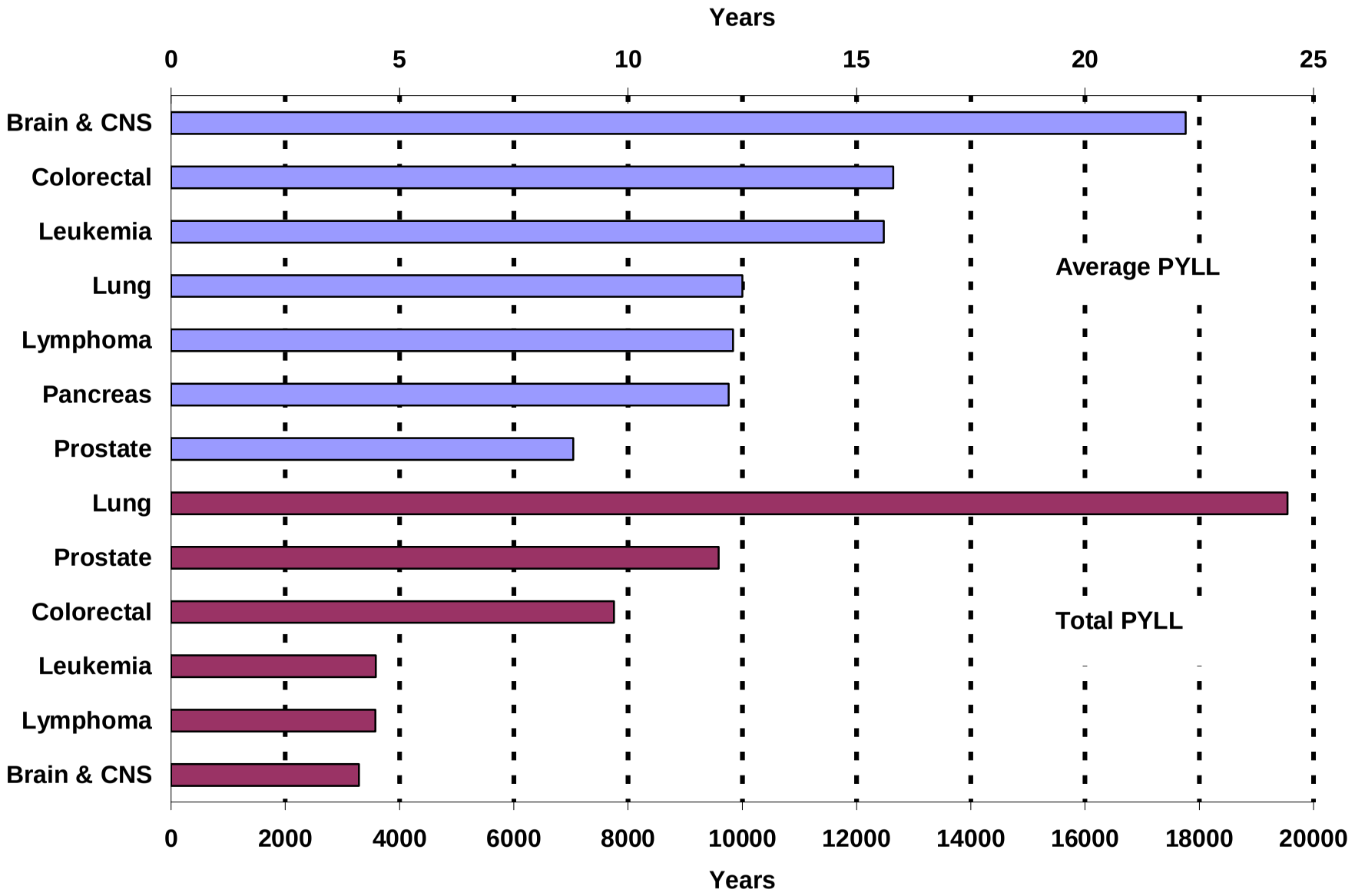

Figure 1.4 Average and Total Person-Years-of-Life-Lost in Males from Cancer in Saskatchewan, 1997-2001

The PSA test became available to physicians in Saskatchewan in 1990. The test itself was covered by provincial health insurance meaning all residents could receive the test free of charge. This is still the case as of 2008. Initially, the Pasqua Hospital in Regina was the only facility in the province able to analyze blood samples for PSA. The Royal University Hospital (RUH) in Saskatoon became equipped to analyze these blood samples a number of years later; however initially most samples were follow-up tests coming from the Saskatoon Cancer Centre for men with known prostate cancer.

In the fall of 1999 the Pasqua Hospital began providing physicians the amount of PSA not bound to other serum proteins, along with the total PSA amount as usual. This unbound PSA is reported to physicians as a ratio of the free-to-total PSA and is known as the free-PSA (fPSA) or free-PSA ratio, which literature has indicated provides an improvement in the sensitivity and specificity when screening for prostate cancer over total PSA alone.[14] Appendix 1 shows the information provided to physicians with each fPSA test result.

The Pasqua Hospital lab provided this additional information for every serum sample where the total PSA was in the diagnostic grey zone of 4.0ng/ml to 10.0ng/ml. This is a grey zone because anything over 4.0ng/ml is considered high but many men will actually not have cancer, while over 10.0ng/ml, cancer is much more common.[15] At the Royal University Hospital in Saskatoon, provision of the fPSA information did not occur. by 1999 however, more serum samples were being sent to the RUH from the community physicians (early detection) and not strictly from Saskatoon Cancer Centre (follow-up of cancer patients). Still, a majority of community-based testing was analyzed at the Pasqua Hospital.

At the Pasqua Hospital the number of PSA samples analyzed grew exponentially from 1990 to 1994. In 1990, approximately 600 tests were analyzed and by 1994 this number grew to over 48,000.[3] Blood samples were coming from physicians from all areas of the province. The sheer volume and the distribution of the referring physicians suggested strongly that the test was being used for screening purposes. In 1995, the Health Services Utilization and Research Commission introduced provincial guidelines for the use of the PSA test. The guidelines, while voluntary for physicians, recommended

against using the PSA test for screening asymptomatic men of any age because the test had a high false positive rate and there was no evidence from randomized trials that early detection of prostate cancer improved mortality.[16]

The number of PSA tests dropped for the first time, but soon after the volume began to increase again to over 80,000 tests (both hospitals) by 2001. Over the same time frame, a corresponding increase occurred in the number of prostate cancers diagnosed. In 1989 there were just over 500 cases in Saskatchewan but by 2001, that number had grown to 840 cases, an increase of over 60 percent.

There are conflicting guidelines available about screening for prostate cancer. In Canada, routine screening for prostate cancer is still not recommended.[17] However, the American Cancer Society promotes prostate cancer screening using the PSA test.[18] In Saskatchewan, the decision to screen ultimately rests with men in consult with their physicians.

1.3 Prostate Cancer: Etiology

The greatest risk factor for prostate cancer is increasing age as shown in Figure 1.1. Autopsy studies have shown that cancer of the prostate may be present in as many as 70% of men over 80 years of age.[19] However, many of these cancers are likely to be clinically latent, in other words disease with histopathologic features of malignancy but with very low potential for growth and metastasis (ability for a cancer to spread to other parts of the body which usually results in death); in other words, cancers with low risk of causing death prematurely. These cancers are fairly common in older men who often die of other causes without ever having a diagnosis of prostate cancer.[20]

Ecologic studies have implicated the "western lifestyle" with increased prostate cancer risk. Studies of migrants moving from areas of lower prostate cancer incidence to areas of higher incidence are often found to assume a risk closer to that present in the new area.[21, 22] This could be brought about by changes in environmental exposures and\or changes in lifestyle including diet. Diet has been investigated as an etiologic factor in numerous studies with mixed results.

Some dietary components are consistently found associated with prostate cancer. High fat intake seems related to prostate cancer but most studies do not account for total energy intake. High fat intake may be related or may represent a low intake of protective

nutrients. As well, fat comes from different sources such as dairy products or meat. Fat from dairy products might be related to increased risk but high calcium intake has also been shown to increase risk as an independent factor, making specific inferences about the role nutrients play in prostate cancer difficult.[22, 23]

Red meat has been shown in some studies to increase risk but the effects of fat or other constituents of animal-fat in foods may be also related to prostate cancer. It is also possible that the intake of meat may not be the cause, but rather the cooking method used to prepare the meat. Charcoal grilling or frying at high temperatures has been shown to produce heterocyclic amines, which are known carcinogens and have yet to be studied in relation to their impact on prostate cancer.[23]

While some dietary components may increase risk of prostate cancer, others may also reduce risk. Some studies suggest that tomato-based foods may decrease risk provided that the tomato is cooked or processed into sauce, soup or ketchup.[24] Lycopene is a strong antioxidant in tomatoes that is more bioavailable when tomatoes are cooked and eaten rather than when eaten raw.[22]

Nutrients such as selenium and vitamin E have shown some promise in reducing prostate cancer risk. Selenium is known to inhibit tumorigenesis (production of new growth) in prostate cancer by several possible mechanisms including antioxidant effects, induction of apoptosis (programmed cell death), immune responses, and effects on testosterone production.[23] Vitamin E or alpha-tocopherol was shown in a Finnish prevention trial to reduce incidence and mortality from prostate cancer by 32 and 41 percent, respectively.[25] The results are encouraging but should be viewed with caution however, since the cohort under study was older male smokers, therefore not easily generalizable to whole populations.

There is good evidence that family history is associated with prostate cancer risk.[22, 23] Men with first-degree relatives with prostate cancer are at greater risk of disease. The risk seems to increase if more than one first-degree relative is affected and if the cancer occurs in ages under 60 years. This increased risk is reflected in some screening guidelines, where men are encouraged to begin PSA testing at younger ages if they have a first-degree relative diagnosed at younger age or if they have multiple first-degree relatives diagnosed at younger ages.[18]

1.4 Prostate Cancer: Methods of Clinical Diagnosis

Prostate cancer is diagnosed in a variety of ways. In older men, the cancer is sometimes clinically identified using transrectal ultrasound without histologic confirmation. Most often however, biopsies of the prostate would be performed to confirm with tissue samples whether cancer was present.

Prostate cancers are also commonly detected at autopsy. The prevalence of latent cancer is very common in older men and is often detected at autopsy even though the cause of death was unrelated to the cancer. Even though the incidence of prostate cancer varies considerably worldwide, there is indication that the prevalence of latent prostate cancer is more similar. This suggests that the initial steps in carcinogenesis may be the same in different populations but differences may exist in factors that promote progression.[26]

Prostate cancer incidence increased steadily during the 1970s and 1980s throughout North America prior to the PSA era. The increase has partially been attributed to increasing rates of transurethral resections (TURP) of the prostate to alleviate symptoms of benign prostatic hypertrophy. Given the high prevalence of latent prostate cancer, increasing numbers of TRUS procedures subsequently lead to more incidental diagnoses of prostate cancer.[27]

1.5 Prostate Cancer: Treatment Options

Men with early stage prostate cancer have more treatment options than most cancer patients. There are four primary treatments that include radical prostatectomy surgery, radiation therapy, hormonal therapy, or watchful waiting. Watchful waiting (close monitoring of disease without radical treatment) is a viable alternative because of the unique epidemiology of prostate cancer. Prostate cancer occurs in older men and in many cases these cancers are slow growing with low potential for metastasis.[28] Watchful waiting may be appropriate for men who will eventually die of other causes. Choosing initial treatment however is difficult given each therapy has their own host of side effects and risks associated with them. Also making the choice difficult is the current lack of evidence that any one of the treatments is better than the others.[29]

Choosing treatment is complex and requires much patient education of the risks and potential benefits. Surgery has the potential to remove the entire tumour in localized

cases but the side effects can include sexual and urinary complications. Men who choose radiation therapy may experience those problems to a lesser degree but are more prone to bowel dysfunction.[30, 31]

Some studies have investigated treatment outcomes for men with localized disease. Local disease has been the focus of study since these represent the vast majority of cases since the introduction of the PSA test in the late 1980s. Harlan and colleagues investigated the factors that predict treatment choice in men from the National Cancer Institute's Prostate Cancer Outcomes Study and found that most men older than 75 years received conservative treatment.[32] Factors associated with conservative treatment after adjusting for age, stage, grade, and PSA level included history of heart attack, unmarried, geographic region, poor pre treatment bladder control, and impotence.

The treatment decision is more complex in younger men with typically at least 10 years of life expectancy. Johansson et al showed that for men who initially had untreated prostate cancer, there was little change in disease progression for the first 10 to 15 years after diagnosis, but after 15 years, there was a decrease in progression-free survival, survival without metastases, and prostate cancer-specific survival.[33] The prostate cancer mortality rate increased by a factor of three after 15 years compared to the first 15 years of follow-up. Radical treatment was suggested as initial treatment for men with a 15 year life expectancy.

A clinical trial investigated the difference in outcomes for men under 75 who had local disease and at least 10 years of life expectancy.[34] Patients were randomized to surgery or watchful waiting. After ten years of follow-up, the surgery group had statistically better prostate cancer-specific survival (30 deaths from prostate cancer compared to 50, respectively) and better overall survival (83 total deaths compared to 103 total deaths in watchful waiting group). As well, the surgery group had lower rates of metastasis development and development of local progression. So while prostate cancer mortality was reduced, this had no impact on overall survival after eight years of follow-up.

Given these treatment choices and the seeming equality of outcomes, the focus for many men with prostate cancer is maintaining quality of life. Each treatment has its own array of potential side effects and men need to be educated about the risks and benefits of

each. Conservative management for men with local disease and Gleason scores (grading scheme for prostate cancer that classifies tumours by their level of cellular differentiation; the scores are the sum of two most dominant patterns each rated on a score of 1 to 5) of 2-4 was found to produce better quality-adjusted life years over radically treated men in a simulation study. For cases with Gleason scores of 5-6, results were similar, and for Gleason scores of 7 to 10, radically treated patients were projected to have better quality-adjusted life years than conservatively treated patients.[35]

Educating men about their options and the risks and benefits of different treatments is required for informed decision making. Sculpher et al showed using discrete choice experiments, that men with at least five years life expectancy, local disease, and who would be eligible for different treatments, were willing to trade off some life expectancy to reduce the burden of some side effects, especially limitations in physical energy.[36] Enabling informed decision making however, requires comprehensive patient education. A recent cross-sectional review of publicly available materials about prostate cancer treatments, risks, and benefits for early stage disease indicates that current education materials do not contain comprehensive information about the risks and benefits of each treatment.[37] This review however was limited to materials available from the internet, print, and multimedia sources.

2.0 RESEARCH PROJECTS

There has been no detailed analysis of the impact of PSA testing on prostate cancer in the Saskatchewan population even though the PSA test has been used for almost 18 years to this point. As well, no study has been done on the utilization of the PSA test in Saskatchewan or what impact was witnessed after 1999 when the fPSA ratio was incorporated. The three research projects described below provide unique insight about PSA use and its impact on prostate cancer diagnosis, relevant not only to Saskatchewan, but to other populations where the test is available free of charge.

The first project takes advantage of individual level recorded data from the labs in Saskatchewan to investigate in detail the testing patterns and test results among men, and about characteristics of physicians who ordered the tests. Very little is reported in the literature about PSA testing at the population level due to unavailability of data. The study provides information about the men tested according to age at time of test, frequency of repeat testing in men over time, geographic variation and as well the distribution of test results for the five-year period 1997-2001. The research also indicates the testing patterns among ordering physicians. The results are based on individual recorded data from population repositories, not survey or clinic\hospital based information. This research provides unique information about the actual use of the PSA test at the population level where the test is freely available to all men.

The second project is an extension of the first project and also takes advantage of individual level recorded data. This study also capitalizes on the natural experiment that took place with the Pasqua Hospital lab, in Regina, Saskatchewan, Canada, that began reporting the fPSA ratio on all serum samples that were in the 4.0ng/ml to 10.0ng/ml range in 1999. The data provides an opportunity to see the immediate impact of providing the additional fPSA ratio information to physicians. Of interest in this study was the comparison of pre and post age-specific biopsy and cancer detection rates given the additional fPSA information. Other than this provision, all else remained the same in Saskatchewan, so changes in practice or outcomes would certainly be attributed to

providing the fPSA ratio. Again, unlike other studies which investigated the fPSA ratio as a supplemental marker for prostate cancer, this research is unique by its population-based focus and universal availability.

The third and final project provides a detailed description of the changes in case mix and treatment patterns that occurred during the PSA era (1990 forward) compared to the time prior to PSA testing. This study indicates the impact PSA testing has had on the key prognostic characteristics such as stage and grade of disease at diagnosis and as well, how treatment patterns have changed in Saskatchewan before and during the PSA era. Stage migration following PSA testing in the population has been well documented in other jurisdictions where PSA testing is common; this work reveals the impact of PSA testing in Saskatchewan. As well, the research shows how the management of the disease has changed in the PSA era. Project 3 reveals how incidence, tumour characteristics and clinical management change in a population exposed to extensive PSA testing.

Much has been written about screening for prostate cancer over the last 10 years. At present, a search of the US National Library of Medicine's PubMed website for articles related to "prostate cancer" and "screening", will retrieve no less than 2700 titles.[38] Two major screening trials are underway investigating the PSA test for screening but so far, no mortality benefit from these trials have been published. In the meantime, researchers are looking at surrogate measures of both benefit and harm from PSA screening. A vast majority of this work however is not population-based, and the circumstances under which men are tested vary considerably. This research provides unique information about PSA testing in a population where the test is universally available free of charge to the patient.

3.0 GENERAL LITERATURE REVIEW

For the purposes of this research, PubMed was searched using the search terms "prostate specific antigen" and "screening".[39] Limits used included being published in last five years, English language, humans, male, and cancer. This generated 861 article titles for potential review. After reviewing the titles and abstracts, 92 articles were included for review. Most of the articles not selected were more focused on very specific biologic or treatment mechanisms and less focused on actually screening or early detection subject matter. Additionally, relevant articles were reviewed from the references in the selected articles.

The articles retained for further review fell into five categories as they relate to this research. The first group of studies reviewed focused on general issues around screening for prostate cancer with PSA based primarily on observational research since on-going screening trials are incomplete. The second group of studies included research that reported on PSA use, or estimates of use, in populations. The third category included studies that investigated strategies to improve the performance of the PSA test, for example using the fPSA ratio. The fourth grouping included studies researching outcomes from prostate cancer screening with PSA. Outcomes were not limited to only mortality reductions, but included other measures such as stage migration and changes in incidence of metastasis at diagnosis. The last category focused on informed decision making for patients. Many of the current guidelines that exist suggest proceeding with PSA testing only when the patient is informed of the potential benefits and as well the potential harms.

3.1 General Screening Issues

The amount written about prostate cancer screening is now extensive and the controversy around screening has not subsided at all over the last 10 years. The debate about whether to do screening using PSA testing stems from the lack of evidence of mortality benefit from two large ongoing screening trials. The Prostate, Lung, Colorectal, and Ovary Cancer Screening trial in the US (PLCO) and the European

Randomized Study of Screening for Prostate Cancer (ERSPC), have both been recruiting men for PSA screening with over 10 years of follow-up.[1, 2] Both trials are expected to publish results sometime in 2009.

The controversy about PSA screening for prostate cancer will remain until some definitive answer about screening is provided from these trials. The trials however are not exactly the same and they might be answering slightly different questions when completed. The PLCO in the US does PSA screening on enrolled men followed by usual care when abnormal tests are generated. There is concern that given widespread use of PSA testing in the US over recent years, the control group is likely to be contaminated by men who are in fact screened.[40] If so, the magnitude of effect will need to be that much greater to find an effect of screening on mortality.[40] The ERSPC however is less likely to suffer from contamination in the control group because PSA use is not as common in the European countries involved in the trial. The ERSPC does have a protocol in place for the follow-up of abnormal tests and indications for biopsy, and so might not be as generalizable to the overall population.[40]

Barry has provided a good description of the screening debate and how PSA has changed the landscape of prostate cancer.[40] The lifetime risk of prostate cancer has changed from 10% to 18% in American men because of increased detection of disease from PSA testing. Although there is greater cancer detection, we still don't know if screening and aggressive treatment will reduce mortality enough to warrant the increase in morbidity that also results from side effects of treatment (sexual dysfunction and incontinence). It has been noted that prostate cancer mortality has recently been dropping, but this varies considerably in US regions and does not necessarily correlate to PSA use in these regions. As well, the UK has seen a drop in mortality as well, where PSA testing is much less common.[40]

It is interesting to note the paradigm shift in clinical care that seems to have occurred with PSA testing and screening. Previously, with mammography, screening was only endorsed and pursued after completion of trials that showed mortality benefit from mammography screening. The notion was as Barry concluded, "don't screen until trials prove its effectiveness". In the case of PSA screening and in particular North

America, the notion seems to be "screen until trials prove it doesn't work, then stop (maybe)".[40]

The debate about screening is very much alive and well, especially in North America. In Canada a very recent debate on the subject was provided by Fradet versus Labrecque and Légaré.[41,42] Fradet claimed in his argument that radical prostatectomy and PSA screening reduces mortality from prostate cancer. Labrecque and Légaré argued that there is minimal effect of radical prostatectomy and that any mortality reductions in the population can't be assigned to PSA testing. They also argued that at this point in time, physicians do not know which prostate cancers are the aggressive ones requiring treatment and which ones will not result in death from prostate cancer i.e. not requiring aggressive treatment. The general practitioner camp also seemed more supportive of informed decision making as long as correct and balanced information was provided to patients.[42]

The arguments were very telling, with urology on one side [43] and general practitioners on the other side.[44] With so much literature on prostate cancer screening available, either side can find articles to support their claims. What is most noteworthy are the different interpretations both sides provide on the *same published research*!

The medical debate has certainly not been confined to Canada. A similar recent debate occurred in the US as well, between urologists Catalona, Loeb and Han versus general practitioners represented by Hoffman from Veteran Affairs.[45, 46] Catalona et al provided a very aggressive stance on PSA screening, not only arguing that the evidence is "convincing" for screening, but that the age of testing should be lowered to 40 years from the current US practice of 50 years. As well they recommend that screening be provided to men over 70 years of age providing they are healthy and that for all cases, the cutoff for abnormal be lowered from 4.0ng/ml to 2.5ng/ml of total PSA. As was witnessed in the Canadian debate, Hoffman claimed the evidence was "unconvincing" and argued against lowering both the age of testing and the threshold for defining "abnormal". Again, both sides reviewing similar research material come to very different conclusions.

Where are these different viewpoints coming from, and what spurs them on? It is hard to argue that some professional groups such as urology don't have a vested interest in treatment of prostate cancer. But we can't paint all urologists with the same brush,

certainly some do not support widespread screening for prostate cancer. So what is the issue, why are there such different opinions? Part of the reason is certainly lack of screening trial evidence, leaving physicians to wade through the evidence themselves and coupled with their own personal beliefs, render a yay or nay on the screening issue. It has been pointed out very recently that of the 19 medical organizations worldwide with recommendations on the issue, only three endorse PSA screening.[47] Two of these three have a conflict of interest; the American Urologic Association and the French Urologic Association, who both recommend annual PSA testing for men over age 50. The other group to endorse is the American Cancer Society but they do suggest testing after discussion of pros and cons with the patient.

One of the main concerns over PSA screening is the possible over diagnosis of prostate cancer. Prostate cancer is very common in men and estimated to be present in 15% to 30% of men over age 50.[48] While many of these tumours would be classified as adenocarcinoma and be considered malignant, many would have low potential for growth and metastasis.[48] In the US alone, it has been estimated from the National Health and Nutrition Survey and data from the PLCO trial that 1.6 million men aged 62 to 85 have a PSA level below 4.0ng/ml and harbor prostate cancer.[49] Given that there is a lifetime risk of 18% for being diagnosed with cancer, but a 3% lifetime risk of dying from it, the potential pool of cases that do not require either diagnosis or treatment is considerable.[50]

Jones suggests that the term "over diagnosis" is in fact incorrect.[51] The literal definition of over diagnosis would be diagnosing more cases than actually exist, which is not the issue. The issue is one of "over detection". Given it is hard to know which cases require treatment to prevent death from those that do not, means many men will be treated needlessly. The clinically relevant cases need to be found, but since we don't know which those are, the approach has been to find all of them. So over detection leads to over treatment and additional anxiety in men.[51, 52] The link between detection and treatment needs to be examined thoroughly. Detection and treatment are very different processes. After detection, in many cases the prudent approach might be to use surveillance where there is low potential for growth or metastasis. Unfortunately many men just end up in treatment due to medical-legal fears of physicians and the attitude of men, who once diagnosed with cancer want it removed regardless.[51] Surveillance, while

legitimate and useful, is also not an easy concept for the general population to understand given a new diagnosis of cancer.[52]

Over detection will apparently remain an issue in Canada for some time. Although the Canadian Task Force on Preventive Health Care in Canada recommends against routine PSA screening for asymptomatic men,[17] the Canadian Urologic Association and the Prostate Cancer Alliance recommend screening only after a discussion of the pros and cons with patients.[50] Regardless, surveys in Canada reveal that half of Canadian men have reported ever having a PSA test.[50] This is not unique to Canada, the same over detection concern exists elsewhere outside of North America as well.[53]

Although over detection is a concern and given that it is not known which prostate cancers would result in death, under diagnosis has also been suggested as a problem. Graif and colleagues conducted a study of tumour characteristics and concluded that under diagnosis was more common than over diagnosis.[54] By lowering the PSA cutoff from 4.0ng/ml to 2.5ng/ml, under diagnosis was reduced from 30% to 26%, while over diagnosis increased from 1.3% to 7.1%. This was also reported in another study looking strictly at tumour characteristics as the foundation of their definitions of over and under diagnosis, and concluded that under diagnosis was more common.[55] Both studies were based in urology clinics. While tumour characteristics are important, the true test of under diagnosis and over diagnosis would be knowledge of deaths from prostate cancer that could have been prevented and non prostate cancer deaths in men who were unnecessarily treated, respectively.

Screening for prostate cancer nevertheless is fairly entrenched in Canada. A survey in Quebec showed that 35% of men 50 to 69 years of age reported having a PSA test, even though there is a lack of definitive proof of benefit.[56] The same survey showed that only 17% of men ever had a fecal occult blood test, even though the evidence shows that colorectal cancer screening is beneficial. The prevailing notion again is that regardless of proof of mortality benefit, many physicians and the public simply just believe the PSA screening is saving lives.[57]

Refinements are already being proposed for how screening should be conducted even in the absence of definitive proof of benefit. Roobol and Schroder looked at the screening interval in two arms of the ERSPC trial comparing two- and four-year intervals

between PSA screens. As expected more interval cancers developed using the four-year screening interval but these were mostly considered non aggressive based on tumour characteristics. Otherwise, there was little difference between cancer detection rates using two- or four-year intervals.[58] This result is potentially important given in the US, screening is largely done annually. Crawford debated this result, not convinced that two- or four-year intervals should be used instead of the annual frequency currently promoted in the US.[57] He points out that there was no randomization of men to either two or four years in the ERSPC trial, but that this was just a comparison of two different study countries that happened to choose different screening frequencies. At the same time he also acknowledged regardless what interval is used; there is no trial evidence of any benefit at this point in time for prostate cancer screening.

Given significant screening levels in North America, much has been written about how to improve the sensitivity and specificity of PSA testing. Thompson et al showed that to find the aggressive cancers early in younger men and to improve sensitivity to 80%, the cutoff for normal would have to be 1.1ng/ml.[59] Their analysis was based on men 55 and over who had a total PSA of 3.0ng/ml or less, so a very select group not likely representative of the general population. Changing the cutoff to such a low level would potentially find more of the aggressive cancers at early stages, but the over detection would be considerable. In the end, the medical community needs to realize there is no "normal" PSA level. It is a continuous marker that can exist at any level. As it rises, risk of cancer rises. At this point, it is very important that patients and physicians work together and discuss very carefully the issues about PSA screening and follow-up before deciding to proceed.[28, 59]

3.2 PSA Test Use in Populations

Not a lot is known about the extent to which the PSA test is used in populations. How frequent is testing in populations, what are the demographic characteristics of the men who are being tested, how close is actual practice to the recommendations that do exist, how has testing changed over time as PSA has become more entrenched in clinical practice, and how do PSA test results distribute in the population? A number of studies have investigated the use of PSA tests trying to answer these questions.

An investigation of the National Ambulatory Medical Care Survey, a representative sample of patient visits to primary care providers in the United States, compared PSA use among men 35 years of age and older from 1995 to 2004.[60] Physicians ordering a PSA test for all types of visits increased from 4.7% to 7% over the time period. For visits that were general examinations, ordering the PSA test increased from 11.2% in 1995 to 32.3% in 2004. PSA testing was found to increase in all men, but more dramatically in African Americans and in young men 35 to 49 years of age.

Veteran Affairs data from the US was also used to investigate PSA use among older men aged 70 years and over who had limited life expectancy.[61] A large sample of almost 600,000 men from 2002 and 2003 was included in the analysis. Fifty-six percent of men were found to have had a PSA test. PSA testing rates did decline with increasing age but did not decline appreciably with worsening health. For men over 85 years of age, 34% in good health had a PSA test, while 36% in poor health were tested. Regardless, no recommendations anywhere suggest PSA testing over 75 years of age, so testing over 85 years of age should be significantly lower than what is practiced among Veteran Affairs.

In Iowa, practice patterns for prostate cancer screening were investigated by mailing a survey to all physicians who care for older men. The response to the survey was 32%. Of those who responded, most general practitioners and urologists replied they stop screening at age 80. It was also found in this research that with increasing age, PSA use declined, but still a group of men over 80 years of age were tested.[62] In another Iowa study based out of a urology setting 5.7% of men over 75 years of age had a PSA test.[63] Konety et al concluded that patients and providers both require education to be more selective about testing men over age 75 to minimize health care costs and unnecessary treatments.

Self reports of PSA use are sometimes used to get prevalence of PSA testing in populations. Chan et al investigated self reports of men attending two different outpatient clinics asking whether they had a PSA test or not.[64] The self report was compared to actual records for sensitivity and concordance. At both clinics, the sensitivity of self report compared to actual PSA use was only about 65%. Concordance at the two clinics was 65% and 88%. Results from such self report studies likely need to be interpreted carefully as in many cases, men are not aware they even had a PSA test.

A hospital-based analysis in Italy extracted records from the lab that served an area of 270,000. The study looked at PSA testing patterns for the period 2002 – 2007. They found many men (18%) over 75 years of age had a PSA test and as well, men under 40 were tested. Most tests were ordered by general practitioners.[65]

Chun et al investigated the distribution of total PSA test results and the fPSA in healthy volunteers with no evidence of prostate cancer.[66] Age-specific median PSA levels were determined. In the youngest age group, 40-49, the median total PSA was 0.7ng/ml and the fPSA ratio was 28%. The median total PSA increased with age group, to a median of 1.8ng/ml for the 70-79 age group. The fPSA ratio did not fluctuate very much by age group and overall was 25%. If the threshold for biopsy was lowered from 4.0ng/ml to 2.5ng/ml, 20% of men would require a biopsy. If the fPSA ratio threshold for biopsy was less than 25%, half of the men would require a biopsy. If the fPSA ratio threshold is lowered to less than 15%, then only 15% of men would require a biopsy.

In Canada, questions about cancer screening behaviour are included in the Canadian Community Health Survey. From this survey, 50% of Canadian men over 50 years of age have indicated ever having a PSA test.[67] As indicated previously, self report estimates of PSA use are likely to be underestimated. Given national guidelines do not support prostate cancer screening; it is nevertheless commonly done in Canada.

3.3 Improving PSA Testing Performance

Different biomarkers have been investigated for over 20 years, but so far none have been as good as PSA for the detection of prostate cancer.[68] The struggle is to find specific prostate cancers that can be treated and death from prostate cancer can be prevented. PSA is generally good at finding advanced cancers but not all high PSA levels means that there is cancer. As well, a low PSA level does not mean cancer is not present.[15] Men with benign prostate disease have been shown to have higher PSA levels compared to some men who have and do not have cancer; as well, younger and older men with benign disease have been shown to have elevated PSA levels compared to men with no benign disease.[69] Although the cutoff most often used for further investigation leading to biopsy is 4.0ng/ml, there really is no cutoff point where you can be absolutely sure cancer is not present.[15, 59] A number of refinements have been suggested to improve the

performance of PSA testing such as PSA velocity, free PSA, age adjusted PSA levels, and PSA density.[68]

PSA velocity refers to the increase in total PSA over time. Increase could be absolute or relative and relevant time periods need to be established. In general, a fast rising PSA would be more indicative of cancer. One study comparing cases of prostate cancer to a screened group showed that for men with cancer, PSA velocity of 2.0ng/ml per year was associated with greater risk of death.[70]

Age-specific reference ranges have been used for some time now and are commonly used in many urology clinics, especially in North America. Given PSA rises with age as does the risk of prostate cancer, it seems natural to have age-specific ranges for further investigation. Age-specific ranges are now being adopted increasingly outside of the United States, such as the United Kingdom.[71] More recently, it has been identified that race plays a role in the distribution of PSA in non caucasian populations, resulting in the development of new age-specific reference ranges that are also race specific.[72, 73] Regardless, no level at any age provides anything close to 100% sensitivity and specificity.

Determining the amount of unbound PSA, or free-PSA in serum has shown to be more discriminating at detecting cancer.[74] The free-PSA ratio (fPSA ratio) is calculated as the percentage of free-to-total PSA. Ratios less than 20% have been shown to be more indicative of cancer while ratios greater than 20% more indicative of benign disease. As with total PSA, there is overlap between the two regions. Originally the fPSA ratio was investigated in the diagnostic grey zone of 4.0ng/ml to 10.0ng/ml because of the considerable overlap of benign and malignant disease in that range. A cost effectiveness analysis done in Spain showed that using the fPSA ratio prior to TRUS guided biopsy was the most cost effective approach to cancer detection, however the effectiveness was sensitive to the cost of the fPSA test and cancer prevalence.[74] As well, this study was in a urology clinic setting, so men involved were already pre selected to attend the clinic because of existing symptoms or conditions such as BPH.

More recently, research has focused on using the fPSA outside the 4.0ng/ml to 10.0ng/ml range and at outcomes at different ratios other than 20%. Pelzer et al used screening volunteers who had total PSA levels in the 2.6ng/ml to 10.0ng/ml range.

Biopsies were used if the total PSA was outside age-specific reference ranges.[75] Prostate cancer detection was then calculated at different ratios, 1-9%, 10-14%, 15-18% and >18%, and at two ranges of total PSA (2.6ng/ml to 4.0ng/ml and 4.1ng/ml to 10.0ng/ml). They found significant differences in cancer detection between the two ranges of total PSA with higher detection in the 4.1ng/ml to 10.0ng/ml range. This would be expected given higher total PSA conveys more risk. When the fPSA ratios were used, the cancer detection was found to be greater in men with a ratio less than 15% between the two groups of total PSA. There was no difference when fPSA ratios greater than 15% were used. A study using frozen sections from the Physicians Health Study and using Receiver Operating characteristics curves showed that combined PSA and fPSA conveyed little improvement in cancer detection or specificity, except for total PSA under 4.0ng/ml, where there showed improvement in specificity of total PSA alone and without losing cancer detection.[76]

In a meta analysis of the diagnostic performance of fPSA and the decision to biopsy, Receiver Operating characteristics curves were again used for all fPSA ratios in the 4.0ng/ml to 10.0ng/ml range of total PSA.[14] Forty-one studies were included on some 19,000 subjects. The 20% fPSA ratio cutoff produced a sensitivity of 93% with only 23% specificity. fPSA was concluded to only be worthwhile in this range at more extreme values of fPSA ratios, under 10%, consistent with other findings that in the diagnostic grey zone of 4.0ng/ml to 10.0ng/ml, the fPSA ratio might need to be lower than 20%.

3.4 Outcomes of Screening with PSA

There is significant PSA screening done around the world in the absence of proof of its benefit. Not surprisingly, a fair amount has been written about outcomes of screening and or the impact of this activity on tumour characteristics and mortality. In the city of Tyrol Austria, the mortality from prostate cancer was shown to have dropped more than the rest of Austria after instituting a controlled screening and treatment program. The program began in 1988, and offered PSA testing free of charge to all men 45 to 75 years of age.[77] Eighty-six percent of men had at least one PSA test in a 12 year period. While the prostate cancer mortality rate dropped in the rest of Austria, the

decrease was significantly greater in Tyrol, which was attributed to screening, down staging of disease, and as well controlled treatment.[78]

Stephens, Trotter, and Martin investigated mortality in the UK for the period 1992 - 2004 and found that there was a larger decline in men aged 55 to 74.[79] Treatments also changed during this time period, with more men having radical surgery and hormone therapy for their cancer treatment. The decline in mortality however pre-dated the widespread use of PSA testing and to some degree the increase in surgery. The observed declines were attributed to diagnosis of earlier stage disease and use of androgen suppression therapy that may have prolonged survival.

Case control studies have been used to investigate mortality benefit from PSA testing as well. In New Jersey, men who died of prostate cancer were matched to live controls without metastatic disease on age, race, and time of exposure to PSA. The screening histories were determined for all cases and controls and no difference was found in screening histories.[80] Another case control study in Washington State matched new prostate cancer cases (diagnosed 1993-1996) on age with controls found through random digit dialing.[81] Self reported data about screening was obtained and follow-up continued to 2007. Fewer men with PSA testing had a prostate cancer death. Although the study suggested mortality benefit from PSA screening, the self reporting of information from participants makes for cautious interpretation.

Preliminary results from the ERSPC have been published looking at surrogate measures of screening effect such as reductions in diagnosis of metastatic disease in men screened.[82] In Sweden after 10 years of screening, there was a significant reduction of 49% in the diagnosis of metastatic disease, but it came with a 1.8 fold increase in cancer detection. The assumption is that diagnosing less advanced disease will result in lower mortality. While this remains to be proven, the issue of over detection and the costs associated with it need to be taken into account.

One of the key early measures of screening effect when screening intensity increases is an observed shift stage distribution. If cancer screening is going to be effective, disease needs to be diagnosed at earlier stages where treatment and prognosis are significantly better. Since mortality benefit has not yet been established for prostate cancer screening, stage shift has been investigated as evidence of a precursor indicator of

future mortality decreases. In Japan, a mass screening program was instituted in the Otokuni District for men 55 years of age and older since 1995. Men who had total PSA test results in the 4.0ng/ml to 10.0ng/ml range had a PSA density determined as the second line test. After 10 years of serial testing, there was a 17% increase in organ confined cancer and a 12% decrease in advanced cancer in the second five-year period compared to the first five years.[83]

Similar findings have been witnessed in many other jurisdictions. Stage migration to more organ confined disease was found to coincide with the PSA testing era in Ohio.[84] This migration then slowed in the later time period of study, which would be expected as part of a screening effect. A similar pattern occurred in Italy over a 15 year period of study, where organ confined disease became more prevalent in the PSA era.[85] Both studies were based on tissue samples from prostatectomy surgeries however, and as such are not reflective of stage migration in the entire population of cases. Surgery would be limited to men generally under 70 years of age with favourable prognosis.

A population-based analysis of tumour characteristics covering 1996 to 2005 occurred in Sweden.[86] Stage migration was seen with more organ confined disease and smaller tumours becoming more common. The age-standardized incidence rate of cases with metastasis at diagnosis also dropped. There was considerable geographic variation around the country in the age-standardized rates of small tumours and in the median age at diagnosis, which was attributed to different PSA testing intensity in those regions.

Aside from stage migration, mortality benefit will only be possible if the effects of treatment make any difference in the outcomes of screen detected cancers. Survival improvements may indicate potential mortality benefits but issues associated with lead time bias and over detection from screening make interpretations difficult. Parker et al investigated the natural history of screen-detected prostate cancer and effect of treatment on survival using data from the UK.[15] The model developed indicated a mortality benefit from radical treatment for men 55-59 years of age if their Gleason score was greater than 7, but there was modest improvement for Gleason scores 7 and no benefit for Gleason scores less than 7. While the result makes sense that benefit would result in cases with more aggressive tumours, it does not mirror what is actually happening in current practice patterns.[15]

3.5 Informed Consent and Decision Making for PSA Testing

Informed decision making about whether to proceed with a procedure or test is not a new concept in the provision of heath care services. As this subject relates specifically to prostate cancer screening however, a whole new field of study has emerged. Prior to 2000, a search of PubMed using the terms "decision" and "prostate cancer screening" produced 32 article titles.[87] For the period 2000 to end of 2007, the same search reveals almost three times as many articles, 86.[88]

The increase in research about informed decision making for prostate cancer screening is understandable. First, since the screening trial evidence of mortality benefit is not in yet, physicians need to be quite careful about proceeding with testing men with PSA where there are so many pros, cons, and controversies associated with it. As well, many of the guidelines that exist, even those that promote PSA screening, advise physicians to council patients individually about the benefits and risks.[89]

In the US, the American College of Preventive Medicine recently conducted a review of literature about PSA testing for screening.[90] After review they determined there was insufficient evidence to recommend routine population-based screening with PSA for prostate cancer. Their official position was that men at higher risk, African Americans, and men with family history of prostate cancer, should be offered information about the potential benefits and risks of PSA testing so that informed decisions to proceed can be made.

The American Cancer Society on the other hand recommends that physicians *offer* the PSA test annually to men over age 50 that have at least 10 years of life expectancy. They also state that men with higher risk should *begin* testing at 45 or even 40 depending on their risk level. At the same time, their recommendations say that no organization in the US recommends routine testing for prostate cancer and they reference the American College of Preventive Medicine recommendations noted above.[91] Finally, the ACS also recommend that health care professionals discuss the benefits and limitations of prostate cancer screening with men to allow for informed decision making at their yearly checkups.

The media plays a large role in influencing decision making, especially in the United States. A random digit dialing survey conducted in the US found that celebrity

endorsements played a role in people's decision about screening using mammography, sigmoidoscopy or colonoscopy, and PSA.[92] The survey had a good response rate of 72% among those known to be eligible and 51% among those who were possibly eligible. Most respondents said they had seen celebrity endorsements about all three modes of screening and 31% of the men said they were more likely to undergo PSA testing after seeing the endorsement. There is likely a similar effect in Canada, given much of our media, especially television, is American based.

These endorsements are certainly not unique to the United States. In Australia, Steginga and Gardiner wrote about the media enthusiasm about prostate cancer screening.[93] They point out that even in the absence of mortality benefit, there should be no surprise about the promotion of screening given there are as many prostate cancer cases diagnosed and deaths as there are from breast cancer in the country. Since no national public health strategy is in place to date, the door is open for advocacy groups to promote screening to the media, who are more than willing to accommodate.

Steginga and Gardiner point out that the prostate cancer screening debate has evolved to include very polarized views, where as constructive debate has often been curtailed.[93] They point out that differentiation between PSA screening of all men and testing after informed consent as suggested by Australian cancer control agencies is very important. Decision aids already exist in numerous formats that can assist men's understanding about prostate cancer, enabling them to make informed decisions. These decision aids however have also been found to make little difference on actual testing behaviour. The informed decision making process needs to be incorporated into primary care, the point where the decision to test is made.[93]

In Canada, a mailed survey was conducted among family physicians in five provinces.[94] The physicians were asked about how patient expectations influences their decision to order cancer screening tests. The response rate was good at 62%. Physicians most likely to order tests for routine cancer screening believed that screening was recommended, while physicians least likely to order the same tests did not believe screening was recommended. However patient expectations or anxiety increased screening among physicians who did not believe routine screening was recommended. The chance that a PSA test was ordered among these physicians went from 28% to 54%

in the presence of patient expectations or anxiety. In the absence of patient anxiety or expectation, the physician belief about screening was the dominant factor predicting ordering of screening tests.

The physician-patient relationship is a critical one for informed decision making about the decision to have PSA screening.[95] Fenton and colleagues analyzed the screening activity among enrollees of a managed health plan in Washington State to see how important the preventive health examination was in determining screening activity.[96] After adjustment for demographics, existing comorbidity and other factors, men who received a preventive health exam were three times more likely to have a PSA test for screening then men with no such exam.

Since physician opinions play a big role in the decision making process, it is very important that they put aside their personal beliefs as much as possible when counseling patients. Physicians who support PSA screening need to acknowledge the limitations and potential risks associated with testing. Conversely, physicians who do not believe in PSA screening need to inform patients of the potential benefits. Only with full disclosure can a patient make an informed decision, regardless of the physician preference.[97]

Katz and Sisler provide an excellent synopsis on the issue of PSA screening from the family physician point of view in Canada.[98] There is a lot of pressure and requirement to inform men about all issues related to PSA testing because we are in a "middle of the road" state on the PSA issue. But informing the patient of all potential limitations and benefits is very time consuming. They point out the office visit might not do anything to persuade men either way if they have their own beliefs based on fear of cancer, positive or negative anecdotes from family or friends, and the influence of celebrity endorsements in the media. As well, prostate cancer advocacy groups promote screening with the goal to find all cancers but the more important outcome should be to advocate for those activities that will result in reduction in mortality, which may or may not happen from just finding all cancers. As well, Katz and Sisler state that the public in general does not trust statistics, which can be interpreted differently or made to look one way or the other. They also admit it is hard for physicians to put their own beliefs aside. Older male family physicians for example, may be more inclined to support prostate cancer screening.

Advocacy groups also promote more counseling time with men about PSA testing. However, the reality for physicians is that another 20 minutes of counseling, in a fee-for-service environment such as Canada, does not make economic sense for the physician. It is easier and better time management to just do the test in the 2 minutes it takes instead of spending 20 minutes trying to inform a patient of all the issues. In the end, men who want screening and believe in it or those who do not want it are not likely going to be convinced otherwise.[98] Family physicians time would be better spent counseling those men who are unsure and do not have a fixed opinion either way. For men who do have their own opinions and expectations, all the physician should do is let them know the consequences either doing the test or not.[98]

Hewitson and Austoker conducted a literature review on the subject of informed decision making, patient information, and the psychosocial impact of PSA testing for prostate cancer.[99] Their review found 24 organizations that had recommendations about prostate cancer screening and only three that endorsed population-based screening; the American Urologic Association, the Canadian Urologic Association, and the American Cancer Society. Regardless of recommendations, they found that men now are more often asking for the PSA test. Publicity about testing and prostate cancer has raised public awareness and helped shape public opinion. As well, it appears that people in general have a belief that prostate cancer can be cured if found early.

An interesting difference has been reported in relation to anxiety about PSA testing in men for prostate cancer compared to women tested with mammography for breast cancer. It has been shown that men have low anxiety levels about PSA testing.[99] Carlsson et al found that men who were having PSA tests had low anxiety levels while having the test, while waiting for test results, and even while waiting for biopsy results.[100]

Hewitson and Austoker's review found that there is much more emphasis now on providing men with balance and relevant information on the subject of prostate cancer screening, to allow for informed decision making. There is evidence that providing information is beneficial, but there is very little evidence about *what* information to supply and even what the general public is able to understand considering the complexity of issues related to cancer screening.[99] Key questions remain unresolved about what information health professionals believe men require, how to present it to them, and what

they are able to understand. As well, it is important to know what the key factors and beliefs are for men that influence their decision making.

Three primary methods used for informing men about PSA testing and screening were identified by Hewitson and Austoker; verbal, written, and video. Verbal communication between men and health professionals has been found to increase men's knowledge about prostate cancer screening in general, and as a result, interest in PSA testing appears to have decreased in these men. This method however requires a lot of physician time. Providing written documentation to men has also been shown to increase their knowledge on the subject. Studies however have not had consistent findings on outcomes resulting from written communication. Some have found that interest in PSA testing decreased in men after reviewing written information on the issues, while other studies found it made no difference in testing patterns. One study found that PSA testing increased significantly with a combination of written information and provision of PSA testing that was free of charge. Using video to present information was also found to be successful at increasing knowledge in general, and as a result interest in PSA decreased in men.

Overall, knowledge about prostate cancer screening increased in men no matter what method was used to provide the information. In general, it was found that interest in screening decreases once the men are informed. It is not known what factors make men change their minds, knowledge about the risk of prostate cancer, the performance of the PSA test, issues about diagnostics or treatment related factors. The most consistent finding is that testing is much higher in men when the PSA test is available free of charge. As well, for men who were seeking out screening, providing information made no difference in their decision to be tested.[101]

4.0 ANALYTIC PLAN

To support the project goals for each of the three projects mentioned in Section 2.0 required consideration of the analytic methods and associated data requirements. Projects 1 and 2 were largely focused on the use of the PSA test in Saskatchewan. *The hypothesis for Project 1 was that there is significant use of the PSA test in the population and that without clear recommendations for its use, considerable variation would exist in the province among men tested by age group, frequency of testing, and geographic location.* As well, it is unknown how PSA test results distribute in a population, although they would be expected to be age-related. The primary interest was how these factors were distributed amongst men who did not already have prostate cancer.

To investigate the hypotheses for Project 1 required population-based PSA data as much as possible. The data also needed to be at the individual level including demographic information to describe the men who were tested. As well, knowledge of their cancer status and dates of diagnosis would be necessary to estimate screening levels among men with no previous prostate cancer at the time of their PSA tests.

Requirements for Project 2 were similar to those of Project 1 with the added requirement for biopsy information. *The hypothesis for Project 2 was that knowledge of the free-PSA ratio would impact the biopsy rate and the cancer detection rate for men who did not have a previous prostate cancer diagnosis and who had a total PSA between 4.0ng/ml to 10.0ng./ml.* The underlying assumption was that knowledge of the free-PSA ratio would better discriminate risk of cancer among these men. If the assumption was true, biopsy rates would either drop with either no change or an increase in cancer detection, or biopsy rates would remain stable but with increased cancer detection resulting from more "appropriate" follow-up.

Project 3 was focused on the impacts of PSA testing on cancer diagnosis, tumour characteristics, and changes in clinical management of prostate cancer that may have been brought about by years of PSA testing. The assumption being that given free availability of PSA testing, screening is commonly practiced in Saskatchewan. If so, *the*

hypothesis would be that in the presence of effective screening, cancer detected would shift to more organ-confined, early stage cases at time of diagnosis. As well, in the presence of screening it would be expected that treatment patterns would change to reflect a higher percentage of early stage cases. More aggressive treatment options are available to men with early stage disease when cure is still a possibility. Therefore *the hypothesis was that with a stage shift, clinical management of prostate cancer would also shift to more radical treatments in Saskatchewan.*

Considerable data requirements were necessary to investigate the hypotheses mentioned above and in Section 4.0. The sources of data and record linkages required are shown in the schematic diagram in Figure 4.1. Projects 1 and 2 required electronic data from the two labs in Saskatchewan capable of analyzing PSA samples. This data had to be linked to data from the Cancer Registry to identify men who had prostate cancer prior to their PSA tests. As well, biopsy data was obtained from pathology departments to ensure there were no missing biopsies performed outside of the fee-for-service structure. The information had to be sent to Saskatchewan Health for further database links to secure demographic information of men tested. As well, billing data was used to secure more biopsy information for procedures that were done through fee-for-service.

Data required for Project 3 was exclusively supported by the Cancer Registry and an extensive chart review that was conducted. As shown in Figure 4.1, the Registry data linked to the PSA data prior to being sent to the Health Department to support Projects 1 and 2. This linkage occurred at two levels, one an extensive linkage of Registry data including cancer data from 1970 to 2002 was used so men with previous prostate cancer could be identified in the PSA data. The chart review data covered a shorter portion of time but included more information about tumour characteristics that could be useful to Projects 1 and 2 as well.

The Saskatchewan Cancer Registry is a population-based registry that has been in existence since 1932. The Registry is considered complete since 1945 and electronic records are available since 1968. The PSA data required for the study came from the Pasqua Hospital in Regina, Saskatchewan, Canada, and the Royal University Hospital in Saskatoon, Saskatchewan, Canada. Linkage of these files was done by the provincial health department, Saskatchewan Health, by using a unique person identifier common in

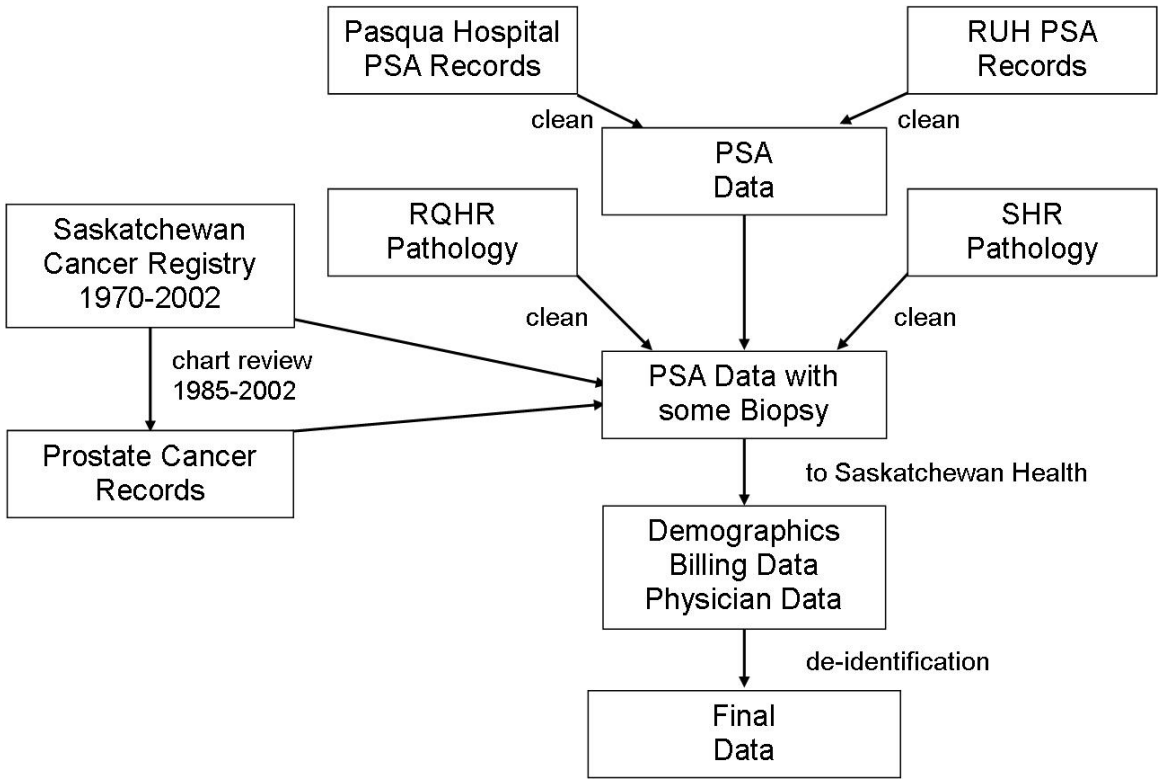

Figure 4.1 Data Sources and Record Linkages

all data sets, the Health Services Number (HSN). The linkage process was done offsite, at Saskatchewan Health and the files returned to the investigator for analysis with the original identifiers removed and new study numbers assigned to each record to preserve confidentiality of information.

A detailed description of each data set follows. Analytic methods were primarily descriptive in nature and are discussed following the description of the data.

4.1 Saskatchewan Cancer Registry

The Saskatchewan Cancer Registry (SCR), which has been in operation since 1932, is one of the oldest population-based cancer registries in the world. Saskatchewan has a stable population of about one million people. In Saskatchewan, cancer is a reportable disease. The SCR prospectively gathers information on all Saskatchewan residents diagnosed with invasive and *in situ* cancers, and has an estimated 99% completeness of case ascertainment for all sites combined.[102]

Information contained in the registry includes patient age, sex, date of diagnosis, dates of follow-up and status at last follow-up. The anatomic site and morphologic type of each cancer are coded according to the International Classification of Diseases - Oncology (ICD-O) system.[103] For prostate cancer, 93.3% of registered cases since 1970 were microscopically confirmed, and for the period 1990 to 1994, this value was 97.1%.[102,104-107] The SCR contains some information on extent of disease and on cancer-directed treatment, but this information is of variable quality and completeness across different cancer sites and over time. Prostate cancer was one of the sites missing this additional information.

Information on deaths in Saskatchewan residents is reported to the Registry on a regular basis by the provincial Department of Vital Statistics, which codes cause of death according to the ICD-10 classification.[108] This information is linked to registered patients.

Follow-up information on all surviving cancer patients in Saskatchewan is obtained by one of two processes. Active follow-up consists of regular visits with a physician at one of the two provincial cancer centres. The frequency and duration of these visits varies according to the type of cancer, its status, and the ability of the patient to come to the clinic for regular appointments. After completion of active follow-up,

patients were referred back to the family physician or referring specialist, to whom annual letters are sent requesting up-to-date information on the patients' status; this is known as passive follow-up, or "follow-up-by-mail". This passive follow-up was temporarily postponed in 2006 while the Saskatchewan Cancer Agency developed a new discharge policy. To date, approximately 170,000 persons have been registered with the SCR, and only 2% have been lost to follow-up.

As mentioned, prostate cancer cases in the SCR were missing important information. There was very limited data about extent of disease (stage) and grade at time of diagnosis, and also limited data about method of diagnosis or first course of treatment. To enhance the SCR's ability to monitor the most common cancer site in the province, a large chart review was undertaken to collect additional information for prostate cancer cases for the period 1985 to 1999 as shown in Figure 4.1. This chart review was supported by a grant from the Saskatchewan Cancer Agency and additionally, a follow-up grant to complete the work. To date, nearly all prostate cancer charts for the time period 1985 to 2002 have been reviewed.

In brief, health records technicians collected information from patient charts under the direction of Dr. David Skarsgard, a radiation oncologist with the Saskatchewan Cancer Agency at the time. A document was created which summarized the rules for data collection. It was continually updated throughout the review as new situations were encountered and new rules were developed so that subsequent cases would be dealt with similarly. Error rates in the data were recorded as type I or type II. Type I errors were those that could have a significant effect on interpretation of the results, e.g. incorrect stage, incorrect grade, incorrect first treatment etc. Initially, the type I error rate was found to be about 5% when random audits were conducted. After resolving errors, the type I rate lowered subsequently, so that overall the error rate in the data is believed to be less than 5%.

Data collected in the review included clinical stage and grade at time of diagnosis. Clinical stage at diagnosis was assigned using information in the chart from as close as possible to the time of diagnosis, before any prostate cancer directed treatment. Clinical stage just before treatment was assumed to be the same as at diagnosis, unless there was information in the chart suggesting otherwise. Clinical stage was assigned using a

simplification of the American Urological Association (sAUA) staging system, A, B, C or D.[109] Designation of substages within the AUA system (e.g. A1 vs. A2, B1 vs. B2) was felt to be impractical and inaccurate because of the variable amount of detail in charts.

For the prostate cancer data in the SCR and in these research projects, stage A refers to clinically and radiologically occult cancer which was biopsy-proven (e.g. by a TURP or needle biopsy). Stage B refers to clinically and/or radiologically detectable cancer which was confined to the prostate. Possible descriptions suggesting stage B include a "*firm* or *hard nodule"* and *"focal* or *diffuse induration"*, with no evidence of metastases. A diffusely firm prostate without focal abnormalities and with no evidence of metastases could be consistent with either stage A or B, so the assigned stage took into account the physicians interpretation.

Cancers with extracapsular and/or seminal vesicle involvement, without evidence of metastases were considered stage C. The lateral margins of the gland were often described as being poorly defined. Other adjectives that were assumed, unless otherwise stated, to describe stage C disease include *"fixed", "grossly irregular", "locally advanced* or *extensive"*, and a "*diffusely rock-hard* or a *huge cancerous prostate"*.

Stage D refers to locally advanced disease that is beyond stage C (e.g. gross invasion of bladder or rectum). It also includes regional (pelvic lymph node) and distant metastases. Pathologic confirmation of metastases was not required, but the treating physician had to have concluded on clinical and/or radiologic grounds that metastases were present and to have managed the patient accordingly.

Gleason score was recorded as a single number (ranging from 2 to 10 out of 10), which represented the sum of the grades (from 1 to 5) of the first and second most prevalent histologic patterns in the specimen. For the purposes of this analysis, the Gleason scores were group as *well differentiated* (Gleason 2 to 4), *moderately well differentiated* (Gleason 5 to 7) and *poorly differentiated* (Gleason 8 to 10) tumours.

Date of diagnosis was defined as the date on which it was first decided that a patient had prostate cancer. Usually that was the date on which histologic confirmation was obtained. This date was already in the SCR but was confirmed during the review. However, if a patient was assumed on clinical and/or radiologic grounds to have prostate

cancer and was managed accordingly before tissue confirmation of cancer, then the date of diagnosis was recorded as the date on which the clinical diagnosis was first made.

The method of diagnosis was recorded. Possibilities included prostatic needle biopsy, transurethral resection of the prostate (TURP), radical prostatectomy, other biopsy (e.g. lymph node, bone marrow), and clinical/radiologic diagnosis. When a patient had more than one diagnostic maneuver on the same day (e.g. TURP and needle biopsy), and both showed cancer, both methods were recorded.

The chart review recorded the first prostate cancer-directed treatment, if any, which was received by a patient at any time after diagnosis. Possible first treatments included radical prostatectomy, radical radiotherapy, hormonal treatment, and no identified treatment (by time of chart review). A very small number of patients were treated initially with chemotherapy. All the Saskatchewan Cancer Agency medical charts were reviewed and contained records of all radiotherapy and chemotherapy, all medical or surgical hormonal treatment, and all radical prostatectomies that were given or performed in the province. Even patients who received some or all of their treatment out of the province usually had this treatment referred to in the Saskatchewan Cancer Agency's clinical notes.

A file was generated of all prostate cancer cases diagnosed in Saskatchewan residents for the years 1985 to 2002. Information obtained from the SCR included date of diagnosis, date of death, cause of death, the health services number (identification number), and morphology. This data was supplemented with additional data elements from the prostate cancer chart review and included stage at diagnosis, grade, diagnostic method, first course of treatment, and all the associated dates. The two sources were linked using the HSN creating one complete file of all the prostate cancer cases. This combined data from the Registry and the chart review provided the necessary information to support Project 3.

4.2 PSA Lab Data

An advantage of studying PSA use in Saskatchewan is that only two labs are currently equipped to analyze serum samples for the whole population (Figure 4.1). As described earlier, the Pasqua Hospital lab in Regina had electronic records beginning in May 1997. Most of the lab data files were archived and had to be de-archived to extract

the data. The Royal University Hospital in Saskatoon only had electronic records beginning in 2001. However, the majority of community-based PSA testing was done at the Pasqua Hospital for this time period. PSA records were obtained for the time period May 1997 to the end of 2001.

Records were obtained from the labs that included the following data: date the serum sample was taken, total PSA test result (ng/ml), patient HSN, patient first and last name, patient birth date, first and last name of the ordering physician and from the Pasqua Hospital, the amount of free unbound PSA (for tests done after October 1999 where the total PSA was between 4.0ng/ml to 10.0ng/ml).

This extraction generated a file containing over 291,000 records. The files contained many duplicate records which had to be resolved. This was a very involved process because of the possibility that men could have more than one PSA test on the same day; therefore records had to be checked for all data elements to determine if it was a true duplicate. As well, the Pasqua lab generated four separate records in the data whenever a reflex test was done to determine the free-PSA amount. These records all had to be reconciled into a single record that contained the total PSA, the free-PSA amount and the ratio for each case.

After the data clean-up, there were still over 230,000 records in the data file representing about 107,000 different men. Many men had more than one PSA test during the study period, many with five or more occurrences. To assist with analysis a count was assigned to each record representing the number of times each man was in the date set. As well, a sequence number was put on each record representing the chronologic order of each test for each man. For example, if a man had six PSA tests, then the count on each of his records was six and a sequence number ranging from one to six was put on each record based on the earliest PSA date to the latest.

Age was calculated for each record in the PSA file as the age at the time of the PSA test. The free-PSA ratio was calculated as the free-PSA amount divided by the total PSA level and converted to a percentage. The data file was then sent to Saskatchewan Health along with the previous prostate cancer file from the registry as indicated in Figure 4.1. At Health, the identifier was removed from the file and unique study numbers

assigned to cases in the same manner as was done with the cancer file from the registry so the files could be linked.

Prior to returning the files, Saskatchewan Health retrieved additional information for the PSA file. The residence of each man at the time of their PSA test was added to the data set. The province is divided into 13 health regions, and for each PSA record the health region was added. As well, biopsy and TURP data was added for each case. These procedures during this time period were largely performed by urologists in the province. Physicians bill Saskatchewan Health fee-for-service based on procedures they perform. These procedures can be tracked and contain the date the procedure was done, the patient HSN, codes for the procedures performed, and a unique ID of the physician who did the procedure.

Saskatchewan Health added additional information to each PSA record as follows. Each PSA record was linked by the HSN to the billing data. If a follow-up procedure of interest (biopsy, TURP, physician visit) occurred in a man within a year after the PSA test and prior to a subsequent PSA test, then the data was included in the dataset.

The cancer file and the PSA file were returned and all identifiers of patients were removed. The study numbers were unique to men so linking the prostate cancer data to the PSA data was possible. Saskatchewan Health also provided a list of all the physician specialties that occurred in the data. The names were reviewed and a physician specialty was assigned to each PSA record. Each PSA record was coded as being ordered by either a urologist, an oncologist, or a general practitioner. There are not a lot of urologists in Saskatchewan so it was possible to review all the names and link a specialty to each record. If the physician was not a urologist or oncologist, it was assumed to be a general practitioner. This assumption would certainly not have been true in every case, as some other physician groups, such as internal medicine etc could have ordered a PSA test. But review of the physician's names revealed that the vast majority were GPs, after urologists and oncologists.

Due to the identifiable nature of the data and the linkages required between datasets from numerous organizations, ethics approval was sought and provided by the Biomedical Research Ethics Review Board from the University of Saskatchewan (REB file # BMC 01-107, Certificate of Approval provided in Appendix 2). Because of the

time it took to obtain data and approvals, extensions for the ethics approval were obtained as required until study completion. As well, the data linkage at Saskatchewan Health had to receive internal approval from the Data Access Review Committee, which was granted albeit after significant time delays.

This research was also supported by a grant from the Health Utilization and Research Commission (HSURC). HSURC no longer exists as the organization changed and the granting portion became the Saskatchewan Health Research Foundation, who continued to support the grant. The money from the grant was used to secure data from the organizations involved and cover the costs of the linkage.

4.3 Methodology

The analysis for the three projects was largely descriptive in nature and is further explained within each project chapter. Denominators for all rates were from the Covered Population of Saskatchewan, an annual publication produced by Saskatchewan Health about population of Saskatchewan residents who are eligible for insured health services (and who therefore are assigned a HSN).[110] The only people not included in the Covered Population are people under federal jurisdiction, such as prison inmates and members of the Federal armed forces or the Royal Canadian Mounted Police.

The primary interest in the studies was to investigate the impact of PSA testing on the incidence of prostate cancer in Saskatchewan and to provide detailed information about how the PSA test is being used. For much of the analysis, the interest was PSA testing in men without known prostate cancer. Linking the prostate cancer file to the PSA file made it possible to see who had a PSA test after a diagnosis of cancer. In much of the analysis, if the date of prostate cancer diagnosis was before the date of the PSA test, then these records could be eliminated from further analysis. For this reason, and due to the survivorship of men with early stage prostate cancer, the prostate file included records dating as far back as 1970.

The 1991 Canadian population was used for age standardization.

5.0 PROJECT 1. WHAT HAPPENS WHEN PROSTATE SPECIFIC ANTIGEN TESTING IS AVAILABLE FREE OF CHARGE IN A POPULATION: THE SASKATCHEWAN EXPERIENCE

5.1 Introduction

Use of the prostate-specific antigen test has been the subject of much discourse over the past 15 years and still conjures significant debate. The utility of the test as a screening tool remains a contentious one with different organizations and countries making different recommendations and taking different approaches with its use. In Canada, screening for prostate cancer (PCa) in the general population is not currently endorsed; however each province has made their own decisions on the availability of the test, since the authority for provision of health services reside under provincial jurisdiction.

In the province of Saskatchewan, PSA tests were introduced in 1990. No restrictions were placed at that time, meaning every resident in the population was eligible for testing at no direct cost to the patient. Most other provinces did not allow such widespread availability. In all provinces now, the test is available for cancer follow-up; in some provinces the test is available as a screening test but at the patients expense.

Given the availability of the PSA test at no cost to patients, use of the PSA test in Saskatchewan increased dramatically from 1990, going from 600 tests in that year to 48,000 tests by 1994 in a population of only one million, of which about 116,000 men were aged 50-79. As was seen in most other industrialized societies, the age-adjusted incidence rate of prostate cancer in Saskatchewan increased significantly, from 104.4 per 100,000 to 154.9 per 100,000 from 1990 to 1993.

It is still not clear whether screening for prostate cancer using PSA provides any benefit to the men tested. Questions about reductions in mortality from prostate cancer screening will hopefully be answered from the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial in the US or the European Randomized Study of Screening for Prostate Cancer.[1, 2] Even in the absence of mortality benefit from screening trials, it is

apparent that screening for prostate cancer is fairly entrenched in many North American jurisdictions. PSA testing has been ongoing for 18 years now in Saskatchewan but how this test is being used in men is not as well known. Fundamental questions remain yet unanswered. How are men being tested at the present time? What age groups of men are being tested? How often are tests done? Are there geographic variations of testing in the population, and how are test results in the population distributed? Who orders most of these tests? These are some of the questions that need to be further examined.

The purpose of this study was to provide a population-based descriptive epidemiologic perspective of PSA use in the province of Saskatchewan where the test is available at no cost to the patient. The hypothesis is that PSA testing is widespread in Saskatchewan and that in the absence of clear guidelines, considerable variation exists in how the test is being used. The goal was to investigate who was having PSA tests and how often. The aims of the study were to estimate age-specific prevalence of PSA testing in men with no previous cancer, as well overall age-specific PSA use, investigate geographic differences of PSA test use, and determine the age-specific range of test results that actually occur in a population-based setting.

5.2 Methods

Saskatchewan has two labs that analyze PSA samples, the Pasqua Hospital lab (PH) in Regina and the Royal University Hospital (RUH) lab in Saskatoon. Records were available at the PH lab going back to the fall of 1997. At the RUH, electronic records were only available beginning in 2001. This study made use of individual PSA records for the period 1997 to 2001 from the Saskatchewan population.

When the PSA test became available in Saskatchewan in 1990, the PH lab was the only one capable of doing the serum analysis. Because of this, all PSA tests, whether for follow-up purposes in cancer patients or community-based tests from general practitioners, went to the PH lab exclusively. After a few years, the RUH lab started to analyze blood samples for PSA, but their primary focus was to provide the service as a follow-up to cancer patients in the Saskatoon Health Region.

In 1997 the PH lab began recording test results in electronic format. Each serum sample had a requisition form associated with it indicating the physician who ordered the test, the patient's name, and the patient Health Services Number. The Health Services

Number is a unique number assigned to each resident of the province, which is to be used when interacting with the health care system.[111]

The PH lab retrieved from its archive database all the PSA records from mid May of 1997 to the end of 2001. The RUH lab did not have electronic records until the year 2001. All records were retrieved from these labs for the period 1997 to 2001 that were in electronic format. For each record, the first and last name of the physician who ordered the PSA test, the first and last name of the patient who had the test, the patients Health Services Number, the date of the PSA test, and the total PSA value in ng/ml was provided.

The PSA data between the two labs was merged into a single file with the same format. Duplicate records defined as those that indicated the same date of the PSA test, same test result, from the same physician, for the same patient were eliminated. A further reconciliation was done for the records from the PH lab. This lab did an additional reflex analysis on every serum sample where the total PSA value was between 4.0 ng/ml and 10.0 ng/ml. If the total PSA was in this range, the same sample was automatically reanalyzed to determine the free-PSA ratio (amount of free (unbound) PSA in that sample). This additional information was sent to the ordering physician along with a guideline for interpretation. This process also generated an additional electronic record in the files. For these cases, the data was converted to a single record containing the total PSA and fPSA amount so it could be interpreted as a single event. The PH lab began this reflex testing process in the fall of 1999.

At the same time a file was generated from Saskatchewan's population-based provincial cancer registry. The Health Services Number and diagnosis dates for all men diagnosed with prostate cancer for the years 1970 to the end of 2002 was obtained from the cancer registry. This file was linked to the PSA file based on the patients Health Services Number that we had from the labs, so we would know whether the men tested with PSA had a prior prostate cancer diagnosis or not.

Another goal was to analyze who was ordering the PSA tests. There would be three main physician types ordering a PSA test in Saskatchewan, general practitioners, urologists, and oncologists. Doctor name associated with each test was obtained and it was possible to identify by name, those who were urologists and oncologists in the

province, since the number of these physician specialties is relatively small and fairly stable. It was assumed all other physicians to be general practitioners even though some could be general surgeons but these would be very few in comparison.

To calculate prevalence rates in the population, the Covered Population counts published annually by the provincial Health Department was used. These counts represent the population of Saskatchewan as of June 30 for each year. For two- and five-year age-specific rates, the population counts were averaged over those years within age groups for denominators.

The merged analysis file was sent to the province's Department of Health and linked to the Personal Registry System to obtain some patient demographic information, most notably, date of birth and place of residence. The Health Department added the demographic information and assigned a unique identification number to each record before returning the files for analysis. The working file had the patient names and Health Services Numbers removed in order to conform to University Ethics Board and Saskatchewan Health Data Access Review Committee approvals.

5.3 Results

To determine the completeness of our data, the reported numbers of PSA tests done by the labs were compared to the data retrieved electronically in our files (Table 5.1a and Table 5.1b). Table 5.1a shows the reported numbers of PSA tests analyzed by both the PH and RUH labs from 1997 to 2001. The RUH did not have a reported number for 1998, so the number was estimated to be 9,100 based on extrapolation of the numbers from 1997 to 1999. Given that estimate, there were 314,511 PSA tests done in Saskatchewan during 1997 to 2001.

The PH lab counted fPSAs (to determine the free-PSA ratio) as a separate PSA test in their counts since it required a separate analysis with more reagent, even though it was on the same blood sample. Table 5.1b, shows the number of records in our files by lab and whether a fPSA was done at the PH lab or not. The data files contained 249,676 records representing 79% of all PSA tests in the province for that time period. Of those, 13,113 PSA tests had an additional fPSA result determined. Those events were reconciled into a single record for cases that had both total PSA results and an additional

Table 5.1a PSA Test Volumes Reported by Labs

Year	PH lab	RUH lab	Total
1997	45,798	3,298	49,096
1998	44,860	9,100*	53,960
1999	47,367	15,068	62,435
2000	51,370	18,208	69,578
2001	58,101	21,341	79,442
Totals	247,496	57,915	314,511

*** estimate based on linear extrapolation between 1997 and 1999 for PH lab, number includes total PSA plus a test for fPSA**

Table 5.1b PSA Tests Provided in Electronic Files

Year	PH lab Total PSA	PH lab fPSA	Total PH lab	RUH	Total
1997	27,106	0	27,106	0	27,106
1998	43,731	0	43,731	0	43,731
1999	46,121	983	47,104	0	47,104
2000	45,836	6,080	51,916	7	51,923
2001	52,705	6,050	58,755	21,057	79,812
Totals	215,499	13,113	228,612	21,064	249,676

Note: the fPSA record coincides with a total PSA from the Pasqua

fPSA result. This resulted in 236,563 PSA records based on total PSA test results in Saskatchewan for the 1997 to 2001 period.

The data for 2000 to 2001 were more complete than the data from 1997 to 2001 because the dataset only included records from the RUH for 2001, but was missing for 1997-2000. To estimate PSA prevalence, men having at least one PSA test for the five years 1997-2001 and for the two-year period 2000-2001 were determined. For the 2000-2001 there were 119,598 PSA tests results available out of a possible 137,806 tests reported, excluding the fPSA tests. Therefore the data represented 86.8% of the PSA testing in the province for 2000-2001. The missing data would certainly not be evenly distributed over the province, but would presumably have mostly been from Saskatoon and surrounding areas.

The 236,563 total PSA test results included men with and without known prostate cancer. These tests were done in 107,037 different men for an average of 2.2 tests per man over the five-year period. The primary interest of this study was the testing in men without prostate cancer at the time of their test. There were 33,321 tests (14.1%) in men with a previous prostate cancer diagnosis. Excluding them from analysis resulted in 203,242 PSA test results where total PSA values were determined. These tests were done in 102,681 individual men.

The age distribution of the PSA tests in Saskatchewan for 1997 to 2001 for men with and without a previous prostate cancer diagnosis is shown in Figure 5.1. A substantial portion (25.1%) of all PSA testing was in men under 50 or over 80 years of age. Among men with no previous prostate cancer, 14.9% of tests were in men under 50 and 9.8% of tests were in men over 80. The median age of men tested who had no previous prostate cancer was 64 years. For all men tested, the median age was 66 years.

For the years 1997 to 2001, 52.1% of the men who did not have known prostate cancer at the time of their PSA test had just one PSA test in the time period (Table 5.2). Many men had more than one test and this proportion increased with age. Most of the men (84%) under 40 who were tested had only one test in the time period. Of the tests done in men 40-49, 40.5% were in men who had more than one test. This increased to 46.2% for the tests done in men 50-59. Of the men in both the 60-69 and 70-79 age groups 59.5% had more than one PSA test in the five-year period. Of note was that a

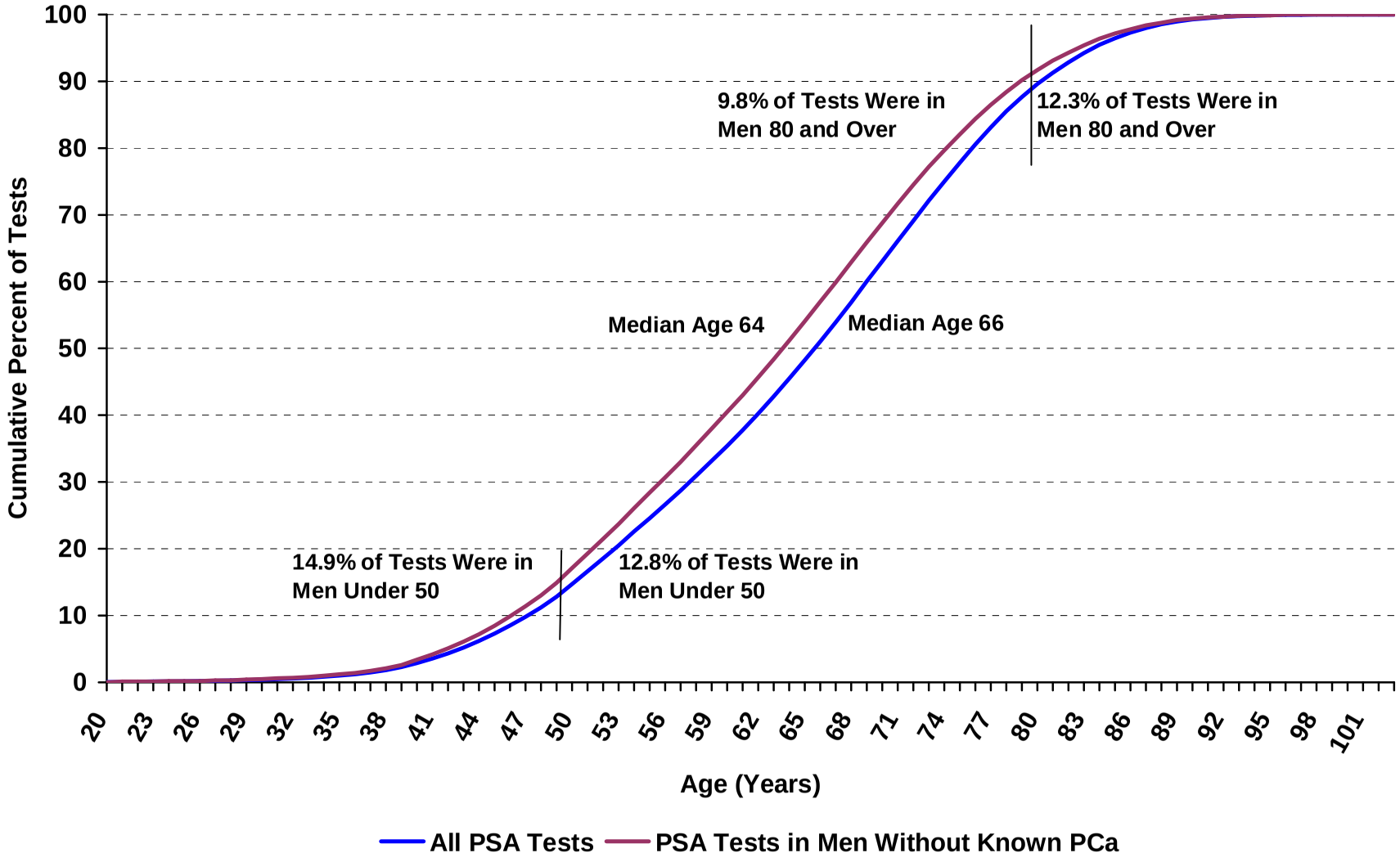

Figure 5.1 Age Distribution of Men Who Had PSA Tests in Saskatchewan, 1997-2001

Table 5.2 Distribution of Men with no Previous Prostate Cancer who had PSA Tests by Age Group and Number of Tests, 1997 - 2001

Frequency of Testing During 1997 - 2001		Age Group*					
Number of PSA Tests	Total Men	< 40	40-49	50-59	60-69	70-79	80+
1	53,507	4,011	12,998	14,374	10,132	7,746	4,246
2	23,968	588	3,729	6,608	6,347	4,619	2,077
3	12,205	114	1,335	3,097	3,776	2,833	1,050
4	6,708	42	422	1,533	2,350	1,822	539
5 or more	6,293	16	216	1,087	2,415	2,048	511
Total Men with at least one PSA Test	102,681	4,771	18,700	26,699	25,020	19,068	8,423

*** age was age at time of first PSA test during 1997 - 2001**

significant number of men (8,423) over age 80 and under 40 (4,771) had at least one PSA test in the five-year period.

As would be expected, the number of PSA tests ordered by urologists increased with age of the men tested (Table 5.3). In the younger age groups, less than five percent of tests were ordered by urologists and most were ordered by general practitioners. Overall 82% of all tests were ordered by general practitioners. Table 5.4 shows the PSA tests ordered for men who did not have prostate cancer at the time of their test. Results show that the older the men, the higher the proportion of PSA tests ordered by urologists. But these proportions dropped markedly when the men diagnosed with prostate cancer were removed from consideration. Overall, most tests (87.3%) were ordered by general practitioners.

The distribution of PSA test results by age group for men who did not have known prostate cancer at the time of their test is provided in Table 5.5. Using a cutoff of 4.0ng/ml to define as a 'normal' test result, we see an increasing percentage of men with abnormal total PSA with increasing age. In the younger age groups less that 50, a very small percentage of men have total PSA above 4.0ng/ml. For men in their 50s at the time of test, 6.7% had an abnormal total PSA. This increased substantially to 18.9% for men in their 60s, 29.1% for men in their 70s and 36.9% for men over 80. Using age-specific reference ranges to define tests as 'abnormal,' for men in their 50s, 60s and 70s the abnormal PSA test results would have been 8%, 16% and 18%, respectively. Using age-specific reference to define abnormal tests would have result in a 38% reduction in the proportion of abnormal tests (29.1% vs 18%) in the 70-79 age group compared to using the overall 4.0ng/ml to define the cut-off for abnormal test results.

Figures 5.2a and 5.2b show the age-specific distribution of PSA test results in men who did not have a cancer diagnosed and in those who had a subsequent diagnosis (within 6 months of the last PSA test). The vertical line in Figure 5.2a reveals both the total PSA level and the cumulative percent of men with no prostate cancer diagnosis at the point where 10% of the prostate cancers had been diagnosed for each age group. In 40-49 year olds, 10% of cancers were diagnosed in men with a total PSA of 1.3ng/ml or less (90% of cancers were higher than 1.3ng/ml). Eighty-eight percent of men 40-49 with no prostate cancer diagnosis had a total PSA result under 1.3ng/ml. Older age groups

Table 5.3 Distribution of PSA Tests by Age of Man Tested and Physician Type (all PSA tests)

	Number of PSA Tests				
Age Group	Urologist	Oncologist	Unknown	General Practitioner	Total PSA Tests
	no., row %	No., row %	no., row %	no., row %	
<40	96, 1.8	2, 0.0	406, 7.6	4860, 90.6	5,364
40-49	683, 2.7	51, 0.2	1524, 6.1	22712, 91.0	24,970
50-59	2665, 5.5	277, 0.6	2558, 5.3	42594, 88.6	48,094
60-69	6773, 10.6	1076, 1.7	3336, 5.2	52439, 82.4	63,624
70-79	10248, 15.7	1680, 2.6	3419, 5.2	50010, 76.5	65,357
80+	4971, 17.1	375, 1.3	1717, 5.9	22091, 75.8	29,154
Total	25436, 10.8	3461, 1.5	12960, 5.5	194706, 82.3	236,563

Table 5.4 Distribution of PSA Tests by Age of Man Tested and Physician Type (excluding men with known cancer at time of PSA test)

	Number of PSA Tests				
Age Group	Urologist	Oncologist	Unknown	General Practitioner	Total PSA Tests
	no., row %	no., row %	no., row %	no., row %	
<40	95, 1.8	2, 0.0	406, 7.6	4858, 90.6	5,361
40-49	655, 2.6	18, 0.1	1519, 6.1	22657, 91.2	24,849
50-59	2297, 4.9	58, 0.1	2518, 5.4	42037, 89.6	46,910
60-69	4497, 7.9	81, 0.1	2991, 5.3	49263, 86.7	56,832
70-79	4918, 10.0	110, 0.2	2674, 5.4	41584, 84.4	49,286
80+	1735, 8.7	34, 0.2	1288, 6.4	16947, 84.7	20,004
Total	14197, 7.0	303, 0.1	11396, 5.6	177346, 87.3	203,242

Table 5.5 PSA Test Results for Men Without Known Prostate Cancer by Age Group, 1997-2001

	Age Group						
Total PSA Result	< 40	40-49	50-59	60-69	70-79	80+	All
LT 4.0 ng/ml	5,323	24,468	43,788	46,107	34,951	12,628	167,265
4.0-10.0 ng/ml	27	304	2,477	8,475	10,336	4,341	25,960
GE 10.0 ng/ml	11	77	645	2,250	3,999	3,035	10,017
Percent Abnormal Using 4.0 ng/ml	0.7%	1.5%	6.7%	18.9%	29.1%	36.9%	17.7%
Total	5,361	24,849	46,910	56,832	49,286	20,004	203,242

	50-59	60-69	70+
Percent Abnormal Using Age-Specific Ranges	8%	16%	18%
Age-Specific Abnormal Reference Levels	3.5 ng/ml	4.5 ng/ml	6.5 ng/ml

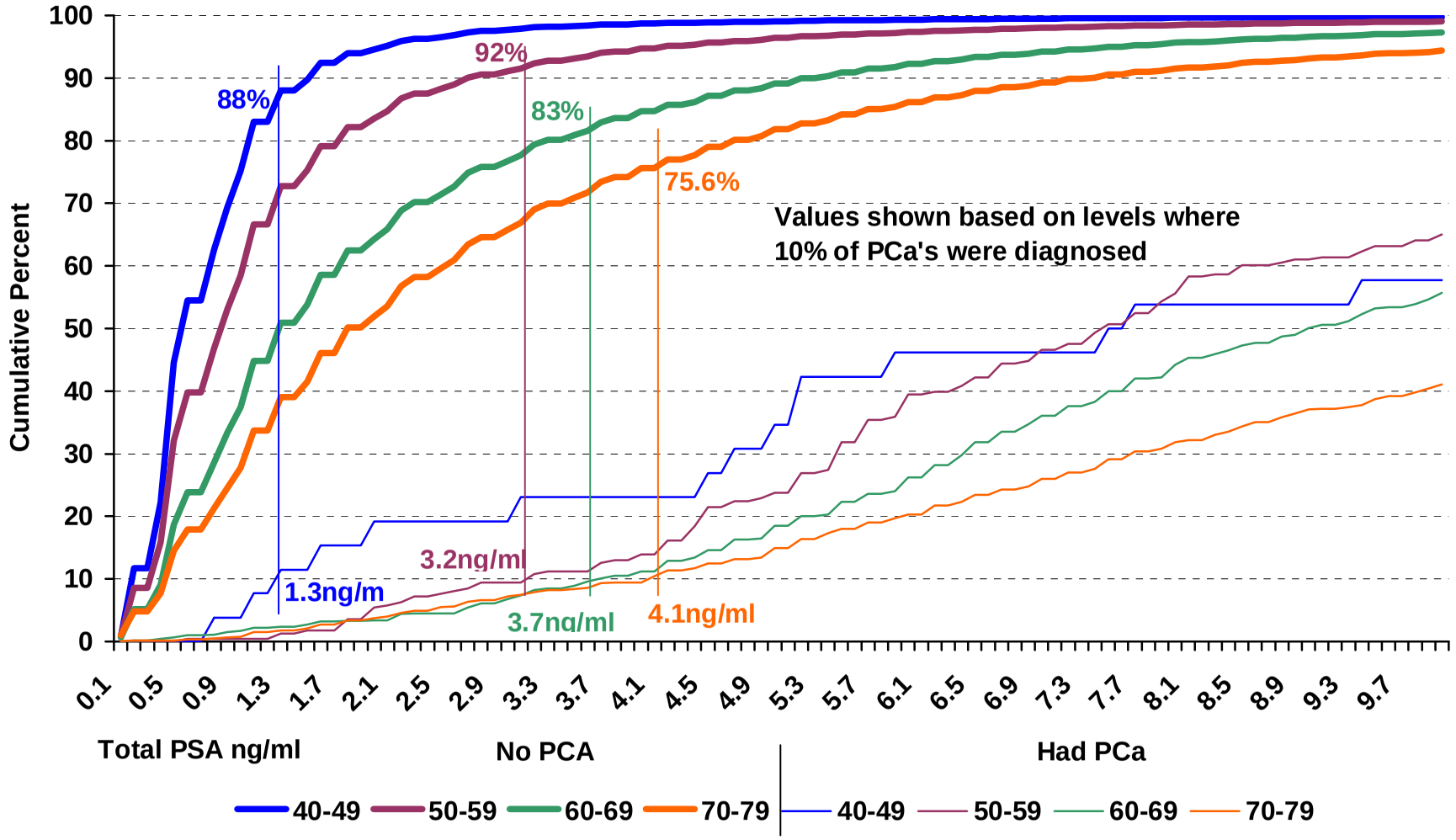

Figure 5.2a Distribution of Total PSA (ng/ml) by Age in Saskatchewan Men Who Had and Did Not Have a Subsequent Prostate Cancer Diagnosis

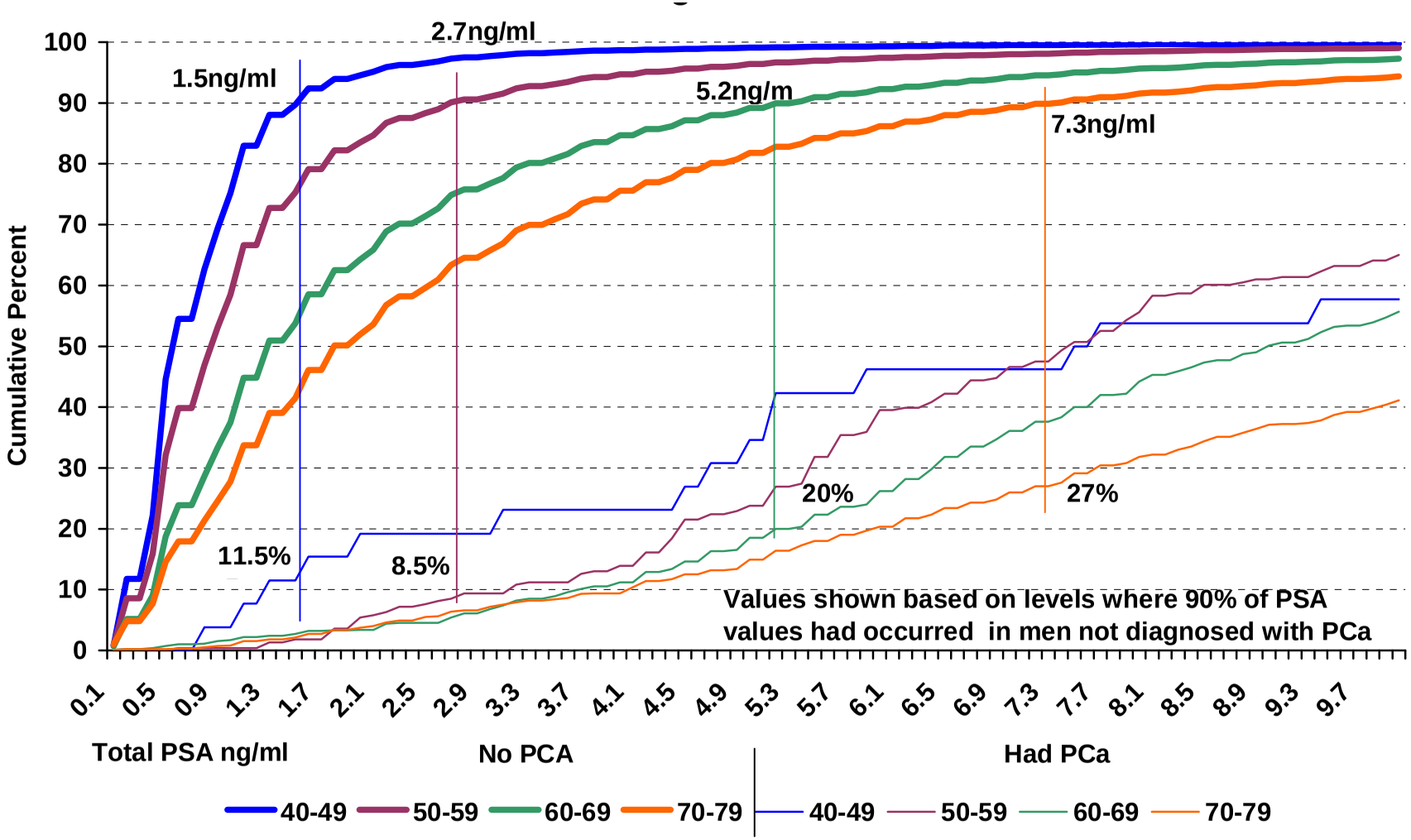

Figure 5.2b Distribution of Total PSA (ng/ml) by Age in Saskatchewan Men Who Had and Did Not Have a Subsequent Prostate Cancer Diagnosis

were associated with a higher PSA level where 10% of cancers had occurred. For men in their 50s, 60s, and 70s the PSA level was 3.2, 3.7 and 4.1 ng/ml. These PSA levels in the older age groups (60s and 70s) accounted for fewer men without a PCa diagnosis, 83% of men in their 60s and only 75.6% of men in their 70s.

The total PSA level and the cumulative percent of men with a PCa diagnosis are shown by the vertical lines in Figure 5.2b, at the points where 90% of the men tested did not have a prostate cancer diagnosis for each age group. For men in their 40s, 90% of men had a total PSA less than 1.5ng/ml and at that level, 11.5% of the prostate cancers had been diagnosed. For men in their 50s, 90% of men without PCa had a total PSA level of 2.7ng/ml or less while only 8.5% of the cancers had been diagnosed. However, for older men in their 60s and 70s, the values were considerably different. Ninety percent of men in their 60s who did not have PCa diagnosed had a PSA level of 5.2ng/ml or less but 20% of men diagnosed in that age group had PSA levels under that amount. Among the 70-79 year age group, 90% of men who did not have PCa diagnosed had PSA levels under 7.3ng/ml, but of the men who had PCa diagnosed, 27% were under 7.3ng/ml.

Figure 5.3 shows the estimated percentage of men who were tested with PSA for the five-year period 1997 to 2001 and the two-year period 2000 to 2001. The proportion of men having at least one PSA test was rather high especially in the 50 and over age groups. At least 60% of men in their 50s, 70s and over 80 had at least one PSA test from 1997 to 2001. For men in their 60s, 58.5% had at least one PSA test. Among men in their 40s, a significant 27% of men had at least one PSA test in the five-year period. When viewed over the two-year 2000-2001 time period, fewer men had at least one test. Even so, at least half the men in the province 60 or older had at least one PSA test over those two years. Thirty-seven percent of men in their 50s also had at least one PSA test in 2000-2001.

The age-specific proportions of men with at least one PSA test for each health region in Saskatchewan for 2000-2001 are provided in a map (Figure 5.4). There was considerable variation in PSA use between the regions. Among the 40-49 year age group, the range was 24.7% in Sun Country to 4.9% in the North. Among 50 year olds, the range varied from a high of 45.1% in Sun Country to a low of 14.6% in the North. The region with the highest PSA tests use for 60 years old men was Sunrise at 58% and

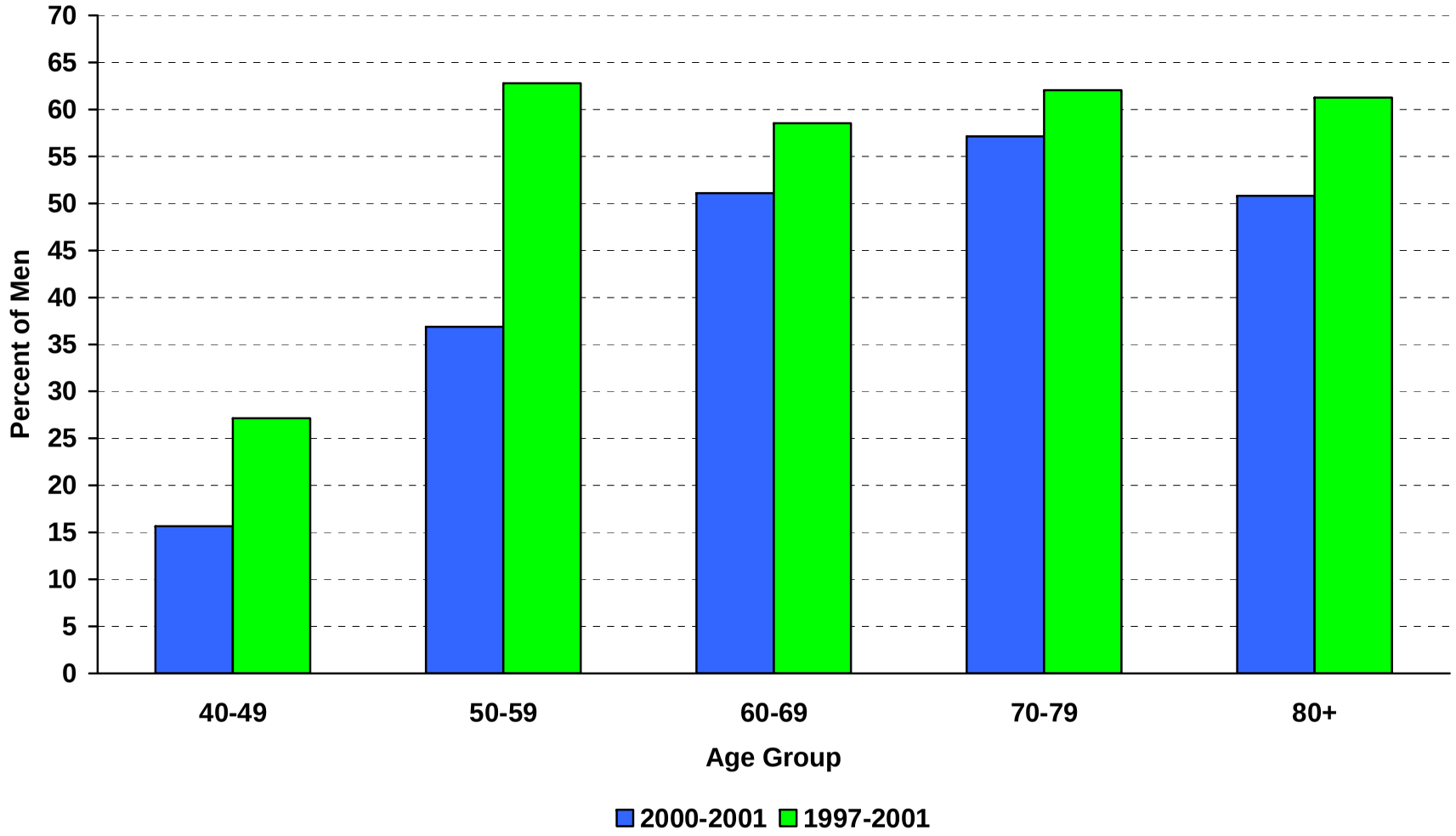

Figure 5.3 Percent of Men in Saskatchewan Who Had at Least One PSA Test in 2000-2001 and 1997-2001

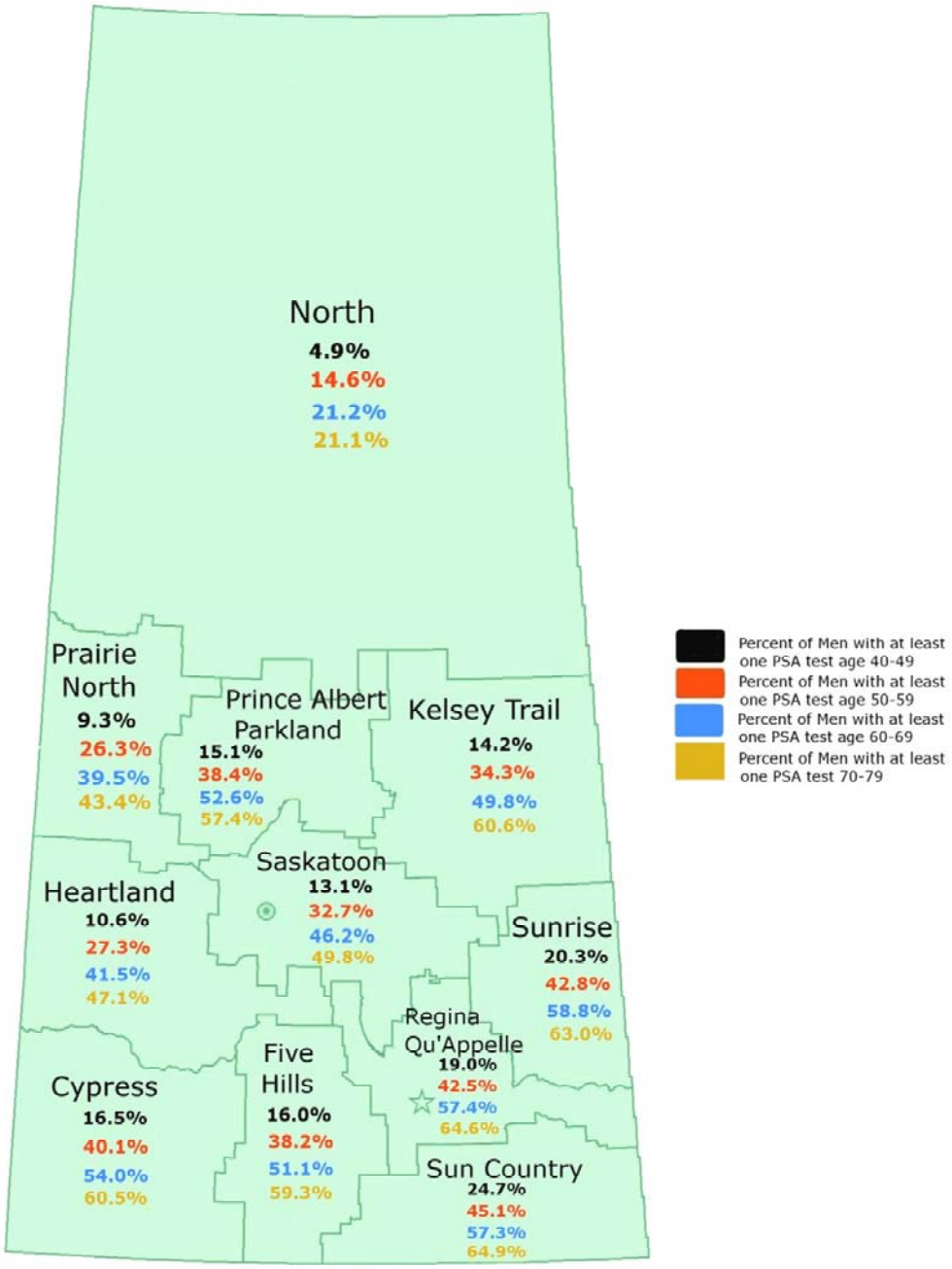

Figure 5.4 Men With At Least One PSA Test by Age Group and Health Region, 2000-2001

the region with the lowest was the North at 21.2%. The North had the lowest PSA use among 70-79 year old men while the highest rate was among men living in Sun Country at 64.9%. Although the North had the lowest PSA test use for all age groups, there was still notable variation among the rest of the health regions with almost a 20% range between the highest and second lowest region. In general, the south and east regions had the higher PSA rates and the north and west regions had the lower rates.

5.4 Discussion

The goal of this study was to investigate the use of the PSA test in the province of Saskatchewan where the test is available free of charge to all residents. This study represented actual PSA data from lab records covering a five-year time period in the population of Saskatchewan. For the entire period, the study was able to obtain 249,676 PSA records covering 79% of the testing in population, making it the most comprehensive population-based study about PSA use to date. When viewed as a two-year period 2000-2001, this study represented almost 87% of all PSA testing done in Saskatchewan.

Investigation of men with urinary or other urinary tract related symptoms warrants further investigation, perhaps using tests such as PSA. This would be fairly common in older men but this does not explain the amount of observed testing in younger men, where prevalence of other non malignant conditions like BPH is very low.[112] Given the number of PSA tests done and the size of our population, a substantial portion of the tests in men less than 50 years must have been done for screening purposes. This is further supported by the fact that a majority of tests (over 90%) were ordered by general practitioners. If most of the "unknown" physicians were also GPs, which is likely, then well over 95% of the PSA tests were ordered by general practitioners. This finding was consistent with other work from the US, showing that the 35-49 year age group had the largest increase in testing between 1995-1999 and 2000-2001 based on survey data.[113]

In Canada PSA screening is not recommended by the Canadian Task Force on Preventive Health Care, receiving only a "D" level of supportive evidence in favour of screening.[114] The Canadian Cancer Society takes a more active stance, suggesting men over 50 discuss PSA screening with their doctor before deciding whether to proceed or not.[115] In the United States, recommendations for PSA screening range from full support

to complete rejection.[116] As well, advocates on the subject have been successful getting their messages out in the media.[117]

Although clear benefits of PSA screening for prostate cancer has yet to be established, PSA testing was found to be very common in Saskatchewan men of all ages. Even the strongest proponents of PSA screening however do not usually endorse testing men over age 75 or in men less than 40.[118] A substantial portion of the tests were found to be done in those age groups in Saskatchewan. Over 27,000 PSA tests were ordered by general practitioners for men less than 50 years of age. Regardless of the guideline considered, in Saskatchewan a considerable amount of PSA testing would have to be deemed inappropriate.

Knowledge of PSA use is critical for understanding changes in incidence and mortality that occur over time and how testing potentially can impact health services.[119] After excluding men with known prostate cancer, an increasing proportion of men with higher PSA levels was found with increasing age group as expected. In the absence of any contrary evidence, GPs in Saskatchewan are likely using 4.0ng/ml as the cutoff for defining test results as normal. In the younger age groups, this resulted in few "abnormal" test results. A big jump occurred from men in their 50s to men in their 60s, going from 6.7% of tests results over 4.0ng/ml to 18.9%, respectively. Almost 30% of men in the 70s had PSA test results over 4.0ng/ml. Urologists are more likely to use age-specific ranges and if adopted by GPs, could make a substantial difference in follow-up and health services by reducing false positive results.

The strength of this study was that PSA events and test results could be assigned to individual men. Studies to date on PSA use have been survey-based or on selected samples which are then used to estimate population testing patterns.[118, 120-123] This study shows that many men in Saskatchewan who did not have a previous prostate cancer diagnosis had more than one test during the study period. As well, multiple testing occurred in all age groups but this was certainly more common in older men.

Knowing who had a PSA test in the population also allowed for more accurate determination of testing coverage and to estimate screening rates. Although PSA testing was found to be very common these results would certainly be slightly underestimated given some missing records for the time period from the RUH lab. The missing records

are more likely to be from the Saskatoon region and are less likely to have been equally distributed throughout the province, so the underestimation probably has a greater effect on the Saskatoon regional rates. Regardless, at least 60 percent of men 50-79 had at least one PSA test between 1997 and 2001 in Saskatchewan. This result indicates slightly greater use of PSA testing than reported by men in the Canadian Health Surveys for PSA testing in Saskatchewan. Surveys from 2000-2001 showed that 58.3% of men aged 45 to 64 and 39.8% of men aged 65 to 74 reported never having had a PSA test. [124,125] Since PSA testing is freely available and indicated on standard requisition forms for blood work, it is certainly possible GPs order a PSA without sometimes patients being aware of it.

There was significant variation in PSA use by health region in Saskatchewan. As shown, most PSA tests are ordered by general practitioners and in Saskatchewan there are shortages of these physicians in some areas, most notably the far north and some of the rural regions. Access to GPs could explain the lower prevalence of testing seen in the North and regions such as Prairie North and Heartland. Saskatoon on the other hand is an urban centre and would not have as significant access issues. Saskatoon more likely is underestimated as mentioned, due to some missing PSA records in the dataset from the RUH hospital. The other potential factor for some of the higher testing rates could be the influence of large group practices in rural areas such as Sun Country. If the philosophy of the group practice is to promote prevention and early detection, they will have a big effect on testing rates in those regions where that GP group might be the "only game in town".

In the neighbouring province of Alberta researchers found much lower PSA prevalence during a random digit dial telephone survey conducted in 1996. Prevalence of PSA testing in men who ever had a PSA test was highest in 60-74 year old men but still only 22%.[126] Alberta however was much more restrictive by not allowing PSA testing for screening purposes. PSA testing in Saskatchewan was certainly higher due to the lack of any restrictions for PSA testing. This is also consistent with other work that has shown insurance coverage increases likelihood of being tested.[122]

The data in this study shows the actual experience of testing in an environment where PSA use is available at no cost to the patient. Although screening is not endorsed,

it is clearly being widely practiced. This research supports the recommendation that it would be appropriate to use age-specific reference ranges for normal values.[127] As shown, choosing an age-specific PSA cutoff above which 90% of prostate cancer cases would be found provides fairly good specificity among men with no cancer, so not too many false positives are generated (1.3ng/ml, 3.2ng/ml, 3.7ng/ml, and 4.1ng/ml, in men 40 to 49, 50 to 59, 60 to 69, and 70 to 79 years, respectively). However, choosing a PSA cutoff level at the point representing 90% of men who did not have cancer (specificity) would result in potentially significant loss of sensitivity among men who have cancer, of as high as 20% and 27% in men 60-69 and 70-79, respectively.

Oesterling et al recommended using cutoffs of 2.5ng/ml, 3.5ng/ml, 4.5ng/ml, and 6.5ng/ml for men aged 40-49, 50 to 59, 60 to 69, and 70 to 79 years, respectively.[127] These values were determined from a study of men with no clinical evidence of prostate cancer and the cutoffs represented the 95th percentiles of PSA in these men. It is difficult to know what the appropriate cutoff should be because it was not known whether men in this Saskatchewan study were diagnosed with the presence or absence of symptoms. Regardless, using Oesterling's et al proposed cutoffs could potentially have resulted in missed cancer diagnosis, since 19.2%, 11.2%, 14.6% and 23.4% of the cancers were diagnosed in Saskatchewan men in those respective age groups and below those cutoff levels. While age-specific reference ranges has merit, they might be required at lower cutoff levels as suggested by this study.

The observation of PSA testing among the age group over 80 is more difficult to interpret. A limitation of our provincial cancer registry is an underestimation of prostate cancer in the older population. Cases with pathology are reported, however clinical diagnoses are the responsibility of the physician to report. The registry does not have large numbers of clinically diagnosed cases but communications with urologists in the province indicates they have many clinically diagnosed cases in their practices, most of which are men over 80 with comorbidities. This would also explain the much higher percentage of PSA ordered by urologists, who are using PSA as a follow-up in these patients. For these reasons, the 80 and over age group was not included in some analyses identified as "men with no previous prostate cancer", because in the oldest age group, that would certainly be inaccurate.

The study has some limitations. The most significant was lack of information about the reason for the PSA test. Certainly some men would be tested to investigate men with symptoms of prostate disease. Benign prostate disease is common, especially in older men, so a portion of the tests would be in this group. As well, some men could be without symptoms but have a family history of prostate cancer and screened as a high risk group. Finally, some men would have been in a low risk screened group. This information was missing making estimates of actual "screening" impossible. What the results reflect is the prevalence of PSA testing in the population, for all reasons combined.

The missing records were also a limitation. Although the study included almost 80% of all the PSA tests for the five-year period, the true prevalence is clearly underestimated. If the missing PSA tests are distributed similarly by age etc and for the same reasons as in the study data set (screening, investigation of symptoms etc), the real population prevalence rates could be as high 75%, since 80% of the total tests produced a population testing prevalence of 60%. It is not known where the missing tests would have come from in the population but most likely the Saskatoon region, which did show lower prevalence compared to the other large urban area of Regina. Compared to the Regina Qu'Appelle Health Region, the prevalence of PSA testing for 2000 to 2001 was indeed about 20% lower in each group for the Saskatoon Health Region.

The data presented represents a five-year window of observation of potentially 18 years of PSA testing. The test began to be used in 1990, so by 1997, it is highly likely that most men would have already had a test. The men represented in the data who appeared only once, certainly could have been tested prior to 1997, so it is not known whether they were experiencing their first PSA test or a subsequent one.

The information from this study is important to our understanding of the optimal ways to use this test in decision making.[123] It is clear that in Saskatchewan, the lack of evidence of screening benefit has been overtaken by lack of evidence of harm. With PSA testing being entrenched since 1990, it is conceivable that testing will continue even if the ongoing screening trials show no mortality benefit. The public is well aware of the test, it is simple to take a serum sample, and the notion that finding cancer early has to be a good thing in all cases will be hard to counteract. Issues of over-diagnosis of cancer are

generally not well understood by the public; for prostate cancer over-diagnosis leading to over-treatment is a very significant medical concern and is very costly to our publically funded health care system.[128]

In the absence of definitive evidence of screening benefit, prevalence of PSA testing in Saskatchewan is high. Since it is now unlikely the test would become an uninsured procedure after 18 years, it is more important than ever to monitor the use of this test and provide feedback to physicians about its potential for both harm and benefit. As well, with actual data in hand, it may be possible to alter what appears to be significant inappropriate testing in younger and older men. Given that the data are available electronically in Saskatchewan and the data linkage capabilities, it would be prudent to form an ongoing single provincial database of PSA records. Such a database would enable timely monitoring of PSA use, and provide excellent research opportunities investigating changes in prevalence of testing over time, individual PSA test results, and tracking practice patterns.

6.0 PROJECT 2. DETERMINING THE IMPACT OF A NOVEL SCREENING APPROACH ON PROSTATE CANCER IN SASKATCHEWAN: THE FREE-PSA RATIO.

6.1 Introduction

Prostate specific antigen (PSA) testing for the detection of prostate cancer, while still controversial, is today well established in clinical practice. Many studies have been conducted investigating additional clinical features combined with PSA testing to improve the sensitivity and specificity of the test. These studies have included such additional measures as determining the prostate volume as it relates to total PSA (density),[129,130,131] changes in total PSA levels over time,[132-138] and determining the free-PSA ratio.

Prostate-specific antigen exists in multiple forms in serum and is predominantly bound to protease inhibitors; however, one form of PSA, free-PSA, is not bound to these proteins.[139] Studies suggest that the ratio of free-PSA to total PSA, or the free-PSA ratio (fPSAr), can better discriminate between prostate cancer and benign prostatic disease than the total PSA alone.[130,140-149] For unknown reasons, the fPSAr is lower in serum samples from patients with prostate cancer than in serum samples from patients with a normal prostate or benign disease. Some evidence also suggests that a lower fPSAr may be associated with a more aggressive form of prostate cancer[139] but others have shown no association with disease stage.[150-152]

PSA testing became available to men in Saskatchewan in 1990. PSA tests are funded by the Saskatchewan Health department and are free of cost to all residents in the province. In August of 1999, the Pasqua Hospital laboratory in Regina, responsible for over 90% of PSA tests in the province at that time, introduced an algorithm for reflex testing for men with total PSA levels in the 4.0-10.0 ng/ml range (Appendix 1). Reflex testing involves a reanalysis of the same serum sample to determine the fPSAr. The advantage of reflex testing is that the same samples which produced PSA levels in the 4.0 to 10,0ng/ml range are reanalyzed, requiring no additional samples from the patient. The

results from the additional fPSAr testing were reported to all service providers who ordered a PSA test after November 1999.

In a literature review and meta-analysis by Roddam et al investigating the diagnostic ability of the fPSAr in men with total PSA in the 4.0 to 10.0ng/ml range, they found that using the fPSAr could reduce the number of unnecessary biopsies while maintaining high cancer detection rate.[153] Few details were available on the methodology of the studies involved and there were not many studies available in the reflex range of interest. As Roddam et al suggested, more research is required about the use of the fPSAr to verify its optimal use.

The purpose of this study was to determine the impact of the reflex testing and the provision of fPSAr test results had on biopsy and cancer detection rates in Saskatchewan. The hypothesis is that the additional information provided with a guideline for additional follow-up would make for more appropriate decision making in terms of who should have a biopsy. Biopsy rates could have no change with an increase in cancer detection or biopsy rates could go down with no change or an increase in cancer detection in Saskatchewan.

6.2 Methods

Only two labs in Saskatchewan currently analyze serum for PSA, the Pasqua Hospital in Regina and the Royal University Hospital (RUH) in Saskatoon. As mentioned PSA testing is fully covered by the provincial health plan. Historically, the RUH only did PSA tests for in-hospital patients or as ambulatory cases prior to 1998. These tests were largely done as follow-up for patients at the cancer clinic located at the RUH. In 1998, the RUH began to do analysis of PSA tests from community providers who largely would be general practitioners using the test for screening purposes. Of all the PSA tests analyzed at the RUH, 50,000 are estimated to have been ordered by community-based practitioners between 1998 and 2001. At the Pasqua Hospital lab, about 248,000 PSA tests were analyzed and it's estimated that about 233,000 would have been of community-based origin for 1997-2001.

Electronic records were only available beginning in May 1997 for Regina and in January 2000 for Saskatoon. Based on the unavailability of Saskatoon records and the time frame of study, only Regina-based PSA tests were considered for study. It has been

estimated that Regina-based PSA tests represent about 82% of all the community-based PSA tests done in the Saskatchewan population for the period May 1997 to December 2001.

Electronic records were obtained from the Pasqua Hospital for the period May 1997 to December 2001. Given that the reflex testing began in November 1999, this provided data for two-and-a-half years before reflex testing and two years two months after reflex testing. In total, 232,923 PSA records were obtained from the Pasqua Hospital lab. It should be noted that during the reflex testing period, when a total PSA was in the 4.0-10.0ng/ml range another record was generated for the free-PSA determination. These records had to be reconciled into one event for each patient. As well, duplicate records that were present were resolved.

Information obtained from the lab included the date of the PSA test, the total PSA result, the free-PSA amount (for PSA tests that had a total PSA of 4.0 – 10.0 ng/ml), the name of the referring physician who ordered the test, and the patient Health Services Number (HSN). The HSN is a unique number assigned to all residents of the province and is used when people interact with the health care system.

The PSA records were linked to the population-based cancer registry housed within the Saskatchewan Cancer Agency. The linking was done by using the Health Services Number. Prostate cancer records were identified in the registry as all cases are coded using the International Classification of Disease for Oncology coding scheme. Data about tumour characteristics such as stage and Gleason scores were retrieved as well as the date of diagnosis and date of birth. In this study date of diagnosis categorized men into two groups. First, the date of diagnosis on which newly diagnosed cases were made after a PSA test, and second, identified men who already had pre-existing prostate cancer at the commencement of the study and were therefore having PSA tests as part of follow-up care.

The linked PSA and cancer data file was then sent to Saskatchewan Health for further linkages. Saskatchewan Health maintains billing records for procedures done in the province, since health care coverage is the responsibility of the provincial government. Procedures such as biopsies, transurethral resections of the prostate, and physician consult visits are billed for by physicians in the province. Procedures are also

specific to physician specialties, for example general practitioners and urologists would have separate billing codes for consult visits. Procedures were obtained if they were within two years after the date of the PSA test and before the date of a subsequent PSA test. The end date for procedures was December 31, 2003.

Saskatchewan Health also maintains a list of all physicians in the province who are licensed to practice and bill for services. The physician name from the PSA file was linked to the physician file at Health to determine the specialty of the physician who ordered the PSA test, specifically whether he or she was a general practitioner or urologist.

Not all procedures in the province are necessarily billed for by all physicians. Biopsies during the period 1997 to 2001 were mostly done by urologists, who would bill for this service. However in year 2000, prostate biopsies began to be referred to radiologists in the two largest centers, Regina and Saskatoon. These procedures would not have been billed for by the radiologists because their service was paid for by the global hospital budgets and was not based on fee-for-service. To make sure the dataset was not missing biopsy procedures, additional data was collected from the electronic systems of the pathology departments in Regina and Saskatoon. These systems identify the tissue sample and the source procedure.

The analysis was limited to men under 80 years of age at the time of their PSA test. There were a significant number of tests in men over 80 years of age and many of these men had over 10 PSA tests each in the five-year study period. This group of men presents an extremely difficult group to have their results interpreted because most would have been clinically diagnosed with prostate cancer and yet a significant number of those cases not registered in the provincial cancer registry. Therefore cancer detection rates, primarily based on pathologic confirmation from cases in the registry, would severely be underestimated for this age group.

Biopsy (and cancer) rates were determined by dividing the number of biopsies (and cancers detected) in men by the number of men who had a PSA test within ten-year age groups. Although a man could potentially be in two age groups over the time period, they were assigned to one age group based on their age at the time of their first PSA test occurrence. Rate ratios were calculated by dividing the biopsy (and cancer) rates during

the reflex testing time period by the rates determined prior to reflex testing. Confidence intervals were calculated for rate ratios using a logarithmic transformation.[154]

6.3 Results

The numbers of PSA tests before and during the reflex testing period are shown in Table 6.1. The numbers of tests in the two time periods are very similar, in fact, once the tests done in men with prostate cancer were eliminated, the number of remaining tests was the same, 92,699. Table 6.1 show that the age distribution of the patients was the same in the two periods of study and that the distribution of total PSA test results was also very similar. In each time period of study, men had more than one test on average and the average number of tests per patient increased as the total PSA test values increased. In fact, there were many men in the population who had many more than one test over the five-year period, some having more than 10 (data not shown).

The focus of the study was men who had total PSA results in the 4.0 - 10.0ng/ml range. Table 6.2 shows the age distribution and number of men who had an index PSA test in the 4.0 - 10.0 ng/ml range prior to reflex testing and during the first two years of reflex testing. The age distribution of men again did not change between the two periods, and the number of men tested between two periods was also similar. This age distribution for those men who had a total PSA in the 4.0-10.0ng/ml range was older than the distribution shown in Table 6.1 for men with any PSA test result. Results shown in Table 6.1 therefore predominantly reflect PSA tests that were under 4.0ng/ml which would include younger men, since total PSA is age related.

Table 6.3 shows the biopsy and prostate cancer detection rates by age group for men who had a total PSA in the 4.0 - 10.0ng/ml range, with and without the fPSAr determined. For the men 50-59 at time of their PSA test, the biopsy rate increased 20% during the reflex testing period and this result was very close to statistical significance (95% confidence interval 0.98 to 1.48). However the cancer detection rate in this age group increased 53% from 57.3 to 87.7 cancers per 1000 men which was statistically significant. In men 60-69, the biopsy rate was unchanged but the cancer detection increased 12% with the fPSAr determination, albeit a non-statistically significant result. In the older age group, 70-79, the biopsy rate actually was reduced 17% which was statistically significant (95% confidence interval 0.73 to 0.95) but this did not affect the

Table 6.1 Age and Test Result Distributions for All PSA Tests in Saskatchewan Before and During the Reflex Testing Process

Indicator	Before Reflex Testing May 1997-Oct 1999 Pasqua Hospital	During Reflex Testing Nov 1999-Dec 2001 Pasqua Hospital
Number of PSA tests	108,794	106,705
Tests done in men without known prostate cancer	92,699	92,699
Age of men tested		
25 percentile	55	54
Median	65	64
75 percentile	73	73
PSA results	(no. tests/no. men)	(no. tests/no. men)
<4.0 ng/ml	74,507 / 53,144	77,274 / 55,015
4.0-10.0 ng/ml	12,976 / 7,822	11,370 / 6,869
>10.0 ng/ml	5,216 / 3,178	4,055 / 2,427

Table 6.2 PSA Result was in the 4.0-10.0 ng/ml Range for Men Without Prostate Cancer at Time of Index PSA Test

Indicator	Before Reflex Testing May 1997-Oct 1999	During Reflex Testing Nov 1999-Dec 2001
Number of PSA tests	12,976	11,370
Number of men	7,822	6,869
Age of men tested		
25 percentile	65	65
Median	71	71
75 percentile	77	77
Age group	Number of men (% of total)	Number of men (% of Total)
50-59	768 (9.8%)	730 (10.6%)
60-69	2619 (33.55)	2131 (31.0%)
70-79	3117 (39.8%)	2796 (40.7%)

Table 6.3 Biopsy and Prostate Cancer Detection Rates for Men with Total PSA in the 4.0-10.0ng/ml Range

Indicator	Before Reflex Testing May 1997-Oct 1999		During Reflex Testing Nov 1999-Dec 2001		
Biopsies by age group	number	rate per 1000 men	number	rate per 1000 men	Rate Ratio (95% CI)
50-59	138	180.0	158	216.4	1.20 (0.98 – 1.48)
60-69	503	192.1	413	193.8	1.01 (0.89 – 1.13)
70-79	458	146.9	342	122.3	0.83 (0.73 – 0.95)
Cancers detected by age group	number	rate per 1000 men	number	rate per 1000 men	
50-59	44	57.3	64	87.7	1.53 (1.06 – 2.21)
60-69	196	74.8	179	84.0	1.12 (0.92 – 1.36)
70-79	201	64.5	174	62.2	0.96 (0.79 – 1.17)

cancer detection, as the rate ratio was 0.96. Historically, before any PSA testing was available in Saskatchewan, a majority of prostate cancers were detected from TURPs done to relieve symptoms of an enlarged prostate. There was no significant change in practice or cancers detected by TURPS before reflex testing and during the first two years after reflex testing began (Table 6.4), which would account for the age-specific cancer detection changes noted in Table 6.3.

Table 6.5 shows the distribution of the fPSAr by ten-year age group. The categories used for the ratios were less than 0.10, 0.10 to 0.24, and greater than 0.24, which reflect the guidelines used by the Pasqua lab with physicians. Of note, the highest percentage of fPSAr test results less than 0.10 (most indicative of cancer) was in the youngest age group 50-59. In all age groups most fPSAr were over 0.24. The percentage of cases in the 0.10 to 0.24 range increased with age from 14.7% of cases in the 50-59 age group, to over 33% of cases in the 70-79 age group.

6.4 Discussion

This research was conducted to investigate the impact on the biopsy and prostate cancer detection rates in an era of determining the fPSA ratio for all serum samples where the total PSA was in the 4.0ng/ml to 10.0ng/ml range in Saskatchewan. The introduction of the reflex testing procedure at the Pasqua Hospital lab to determine the fPSAr automatically for every total PSA test result in the 4.0-10.0ng/ml range had a significant impact on both biopsy and prostate cancer detection rates. The difference was age-specific, with the greatest impact on the younger men, specifically in the age group 50-59 years at the time of testing. In this group, the biopsy rate increased 20% but the cancer detection rate showed an impressive relative 53% increase. For younger patients, reflex testing had a clear beneficial effect by better discrimination of malignant from benign disease at biopsy and by overall better detection of prostate cancer.

One reason for this was the 50-59 age group had the highest percentage of fPSAr under 0.10 resulting in more “appropriate” biopsies in this group than would have happened in the absence of the fPSAr. The percentage of men with fPSAr less than 0.10 decreased with increasing age, implying that the free unbound component of PSA is increasing more rapidly than the rate at which total PSA is increasing with age. This

Table 6.4 Prostate Cancers Detected by TURPs for Men with Total PSA in the 4.0 - 10.0 ng/ml Range

Age Group	Diagnosed from 1997 to 1999	Diagnosed from 2000 to 2001
50-59	6.2%	7.6%
60-69	15.0%	13.1%
70-79	25.6%	22.9%

Table 6.5 Distribution of fPSA Ratios (percentage of cases) by Age Group

Age Group	Ratio Less Than 10%	Ratio Greater Than or Equal to 10% and Less Than 24%	Ratio Greater Than 24%
50-59	17.8%	14.7%	67.6%
60-69	12.3%	19.8%	67.9%
70-79	8.8%	33.7%	57.5%

suggests that age-specific reference ranges for fPSAr are likely required to reflect similar age-specific reference ranges suggested for total PSA results.

The impact however was not limited to the 50-59 age group. While less dramatic, the biopsy rate for men in the 60-69 age group was unchanged, still a 12% increase in cancer detection was realized for men who are 60-69 years with reflex testing. In the 70-79 age group, cancer detection was unaffected but the biopsy rate decreased 17%. The guidelines and information provided by knowing the fPSAr in all cases increased overall cancer detection 8.7% for all ages combined (50-79) while reducing the overall biopsy rate 4.7%.

There are additional costs associated with using the reflex methodology. Since every test in the total PSA range of 4.0ng/ml to 10.0ng/ml was automatically re-analyzed for fPSA, the men who had prostate cancer with this level of total PSA would have had a fPSA determined even though for them, it is not useful information. Analysis of the records shows that in the 26 month period where fPSA was determined, just over 2200 PSA tests had an fPSA done in men already known to have prostate cancer or about 1100 unnecessary fPSA tests per year. Currently there is no way for the lab to know if the serum being analyzed is in a man with or without prostate cancer and it could be that the marginal cost-benefit is such that current processes are adequate.

In Saskatchewan, as in the rest of Canada, population-based prostate cancer screening is not endorsed by the Canadian Cancer Society.[155] However, the evidence would indicate current practice is actually in favor of screening. Saskatchewan had a population of one million people in 1999, the middle year of the study period. Of this, 148,348 were men aged 50 plus and 119,937 were aged 50 to 79.[156] In 1999 there were 62,435 PSA tests analyzed in Saskatchewan. by 2001, over 80,000 PSA tests were performed. Given these testing levels, population size, and the classic screening effect observed in age-adjusted rates after introduction of the PSA test in Saskatchewan as shown by Skarsgard and Tonita, significant prostate cancer screening is apparently being undertaken in Saskatchewan.[3] Therefore, results of this study reflect the impact of determining the fPSAr for a population that is essentially experiencing extensive screening. Unlike other published studies investigating the utility of fPSAr which are largely hospital or urology practice-based case control designs,[139,157-160] this study reflects

the impact at the actual population-level of incorporating the fPSAr to all cases where the total PSA was in the 4.0 to 10.0ng/ml range.

Some studies have also investigated whether the fPSAr can better predict extent of disease at time of diagnosis.[150-152] These studies did not show there to be any benefit of knowing the fPSAr for staging of disease, they also did not have large numbers of cases to use for analysis. Sakai et al had 147 prostate cancer patients and Aslan et al only 42 to investigate stage and the fPSAr relationship. This study had over 850 cancer cases diagnosed during the study period. Analysis of the stage of disease showed no change in any of the age groups before or during the fPSAr era. In all age groups, the vast majority of cases were organ-confined. Although improving cancer detection, it does not appear that knowing the fPSAr has any additional benefit for determining the extent of disease.

Gleason scores were also investigated in the cancer cases diagnosed. What was interesting to note was a shift in the fPSAr period to more moderately differentiated cases from well differentiated cases. In all age groups, the percent of cases moderately differentiated increased on average from about 63% to 84%. This finding is difficult to interpret in relation to the fPSAr. As a check, Gleason scores were also investigated for prostate cancers diagnosed during the same period but outside the 4.0- 10.0ng/ml range. While not as consistent in all age groups, a similar shift to more moderately differentiated cases was found in the other total PSA ranges (less than 4.0 and greater than 10.0ng/ml). The shift is less likely a result of the fPSAr and more likely the result of ongoing screening activity and the fact that more men in the fPSAr period would have been more likely to have had multiple tests. Reasons for clinical investigation with multiple tests could have been due to changing total PSA levels, which may be more closely related to grade.

Elabbady and Khedr[161] investigated Gleason scores in 62 prostate cancer cases to see whether there was a relation between fPSAr and higher and lower Gleason scores (Gleason scores 7-10 and 2-6, respectively). They concluded that men with lower fPSAr had higher risk of elevated Gleason scores. In 353 cancer cases diagnosed with fPSAr's in this study, 27% had high Gleason scores and a fPSAr less than 0.15, 15.7% had high scores and fPSAr between 0.15 and 0.20, and 32% had high scores in the fPSAr range greater than 0.20. The percentage of cases with the lowest fPSAr and the highest fPSAr

had very similar distributions related to higher and lower Gleason scores, suggesting no relation between the two factors.

Incorporating the reflex methodology for the fPSA was like exposing the population to a natural experiment. It happened at a point in time and throughout the population and no other changes occurred. The primary limitation that could have influenced the results witnessed was repeat testing. Men in the second time period (during reflex testing) could have had more previous PSA tests then men in the first time period prior to reflex testing, so the reason for biopsy may have been unrelated to the fPSA and more related to changes in total PSA over time. It is certainly true that in the dataset, the two groups were not independent of each other. Some men would have had PSA tests in both periods and could be represented therefore in each group.

Again, the data did not have reasons for the PSA testing, so this impact is not simply in the screened group, but among all men tested for all reasons. Since PSA testing had been in Saskatchewan since 1990, seven years before the study period began, it would seem reasonable that even men in the first part of the study period (without reflex testing) had considerable access to previous tests and were not likely much different than the men tested during reflex period.

The data in this study covers a time period that begins in 1997 and concludes at the end of 2001. However dated, it demonstrates the impact of determining the fPSAr at a population level, and with significant numbers, which is unique. At present, the labs still operate using the same methods and the level of PSA testing in Saskatchewan remains high. Updating the data with more years would allow for further analysis and would become a very valuable and unique source for research on population-based PSA testing.

7.0 PROJECT 3. CHANGES IN CASE MIX AND TREATMENT PATTERNS IN PROSTATE CANCER IN SASKATCHEWAN DURING THE PROSTATE SPECIFIC ANTIGEN TESTING ERA

7.1 Introduction

The changes in incidence of prostate cancer have been significant since the prostate specific antigen test began being used for early detection purposes. The debate about screening using the PSA test continues because of the lack of definitive proof from randomized trials that screening will reduce mortality from prostate cancer.[162,163] Consequently, numerous retrospective studies have been completed investigating the impact of PSA testing on incidence, case mix changes, and mortality in an attempt to understand the usefulness of this test.

In earlier work we showed the impact PSA testing had on the incidence, mortality, and survival of prostate cancer in the province of Saskatchewan in Canada.[3] Saskatchewan is unusual in North America because all residents of the province have access to health care through the provincially funded health plan and the PSA test is insured under that plan, making it free of charge to all men. The PSA test became available to men, in Saskatchewan in 1990. The impact of PSA testing on incidence was immediate, as the age-adjusted rate increased 60% from 96.4 per 100,000 in 1989 to 153.9 per 100,000 in 1993. Then from 1994 to 1997 the incidence dropped, returning closer to the trend established before 1990. This pattern is indicative of a screening effect resulting from the introduction of PSA testing. During the PSA era, survival of diagnosed cases improved but mortality rates remained steady indicating a lead time effect from the earlier diagnosis of cancer.

These changes in incidence of prostate cancer with the introduction of PSA testing are consistent with alterations in the case-mix of the disease, with tendency for increased diagnosis of earlier staged cases. Stage migration, meaning a tendency to detect disease when it is in earlier stages of development is an indicator of the effectiveness of a screening test, and consequently, it may predict an eventual reduction

in mortality as well.[164] Diagnosing cases earlier has been reported in other jurisdictions where the PSA test is used, but most studies are not population based.[165-168] We were unable to confirm a stage migration in our previous study because of a lack of reliable information on tumor characteristics in the provincial cancer registry. Changes in case mix could also result in changes in treatment, but again the provincial cancer registry does not contain complete information in this area.

The hypothesis is that PSA testing in Saskatchewan has shifted the stage distribution of prostate cancers detected to more organ confined cases and consequently that changes in clinical management of the disease has resulted. The purpose of this study was to describe the changes that occurred in the case-mix and in treatment patterns for prostate cancer in Saskatchewan after the introduction of the PSA test in 1990.

7.2 Methods

A detailed description of the Saskatchewan Cancer Registry (SCR) is available elsewhere.[3] In brief, cancer is a reportable disease in Saskatchewan. Pathology reports are sent to the SCR if there is any mention of in situ or invasive cancer. The anatomic site and morphology of each cancer is coded in the SCR using the International Classification of Diseases–Oncology (ICD-O) system.[103] The SCR contains dates of diagnosis, patient demographic information, and dates of follow-up. Information on date and cause of death comes to the SCR from the provincial Department of Vital Statistics on a regular basis. Death information is coded using ICD-10 classification.[169] We included only the deaths where prostate cancer was the primary cause of death in calculations of mortality rates.

Extent of disease and treatment information for prostate cancer was not available in the SCR. We conducted a large chart review to provide information on tumor characteristics and treatment for all men diagnosed with prostate cancer in Saskatchewan from 1985 through 2001, a period spanning the introduction of PSA testing in 1990. We identified, within the SCR, all cases of prostate cancer for these years.

Our intent was to study prostatic adenocarcinomas, which represent about 97% of neoplasm's involving the prostate gland. We therefore limited our analysis to ICDO-M morphologic codes 8140 (adenocarcinoma), as well as 8000 (neoplasm not otherwise specified) and 8010 (carcinoma not otherwise specified), a group of cancers which will

subsequently be referred to as prostatic adenocarcinoma, or prostate cancer (PCa). We included the latter two categories of poorly-defined cancers in the above group because, in the absence of any information suggesting otherwise, the overwhelming likelihood was that they were adenocarcinomas.

The extraction generated 10,691 total prostate cancer cases for the time period 1985 to 2001. Of these, 10,361 (96.9%) had the morphologies of interest and we were able to review 10,018 (96.7%) of the eligible charts. A modified American Urological Association staging system was used to establish extent of disease at the time of diagnosis. Stage A was clinically occult, B was cancer limited to the prostate, C included local extension, and stage D was metastatic to lymph nodes, bones or other distant sites. Other information collected from the review included, Gleason score, PSA level at diagnosis, method of diagnosis, and information specific to the first course of treatment, and follow-up status at time of chart review.

The charts were reviewed by trained health records technicians under the supervision of a radiation oncologist (DS), who also reviewed all charts during the training period. To assist the technicians, a detailed set of rules for data collection was produced and regularly updated as new situations were encountered to ensure all cases were dealt with consistently. The technicians were also able to send charts to the oncologist for review and clarification if they had questions. As well, a random audit was done on approximately 20% of charts by the oncologist to establish error rates in the data. Errors were also corrected if found. Based on the audit and corrections, the error rate for stage and Gleason score is estimated to be three percent or less in the entire dataset.

The provincial health department maintains population files for residents who are eligible for health services. These population files provided the denominators to calculate age-specific rates. Age-adjusted rates were standardized to the 1991 Canadian population.

7.3 Results

Figure 7.1 is an update of earlier work with the addition of the years 1998-2001. The age-adjusted incidence of prostate cancer increased substantially again during the 1997 to 2001 period, corresponding to another large increase in PSA testing in Saskatchewan. by 2001, the age-adjusted incidence reached the peak levels witnessed in

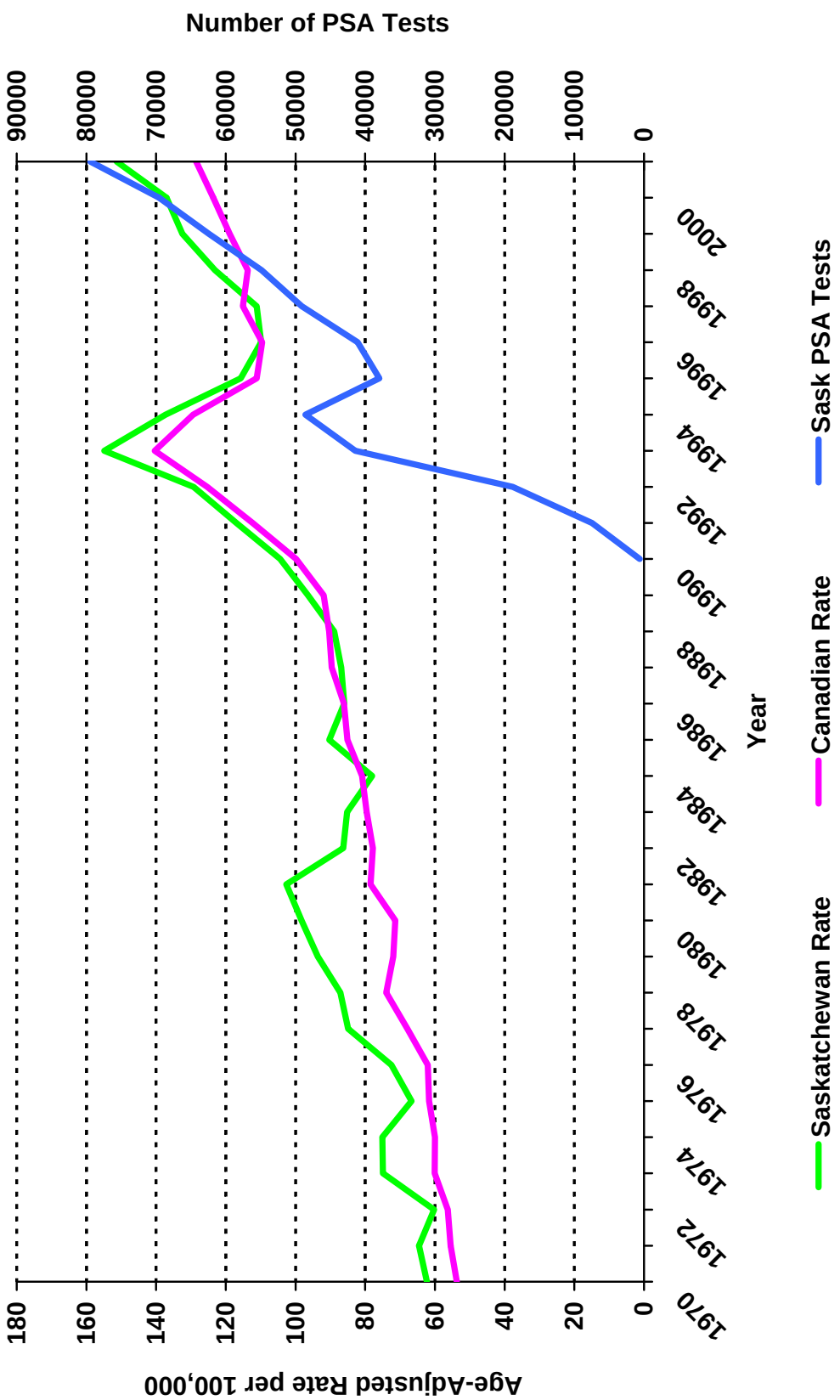

Figure 7.1 Age-Adjusted Incidence Rate for Prostate Cancer and PSA Volumes in Saskatchewan, 1970-2001

1993. The pattern was similar in Canada, although the peak level in 1993 was somewhat lower than in Saskatchewan and the data point for 2001 is an estimated value.[170] In Saskatchewan, just about 80,000 PSA tests were done in 2001; almost double the number from 1993.

For the entire time period 1985 to 2001, 27.0% of cases were Stage A or clinically occult, 36.9% were Stage B or limited to the prostate gland, 12.0% had local extension (Stage C), and 15.4% had metastases at diagnosis (Stage D). Some cases (2.8%) were known not to be Stage D and 6.0% could not be staged at all. Fifty-two percent were moderately differentiated (Gleason scores 5, 6, 7), 28% were well differentiated (Gleason scores 2, 3, 4), 14.5% were poorly differentiated (Gleason scores 8, 9, 10), and 4.7% had unknown grade.

The age-adjusted rate of prostate cancer at Stage A did not change over the time period 1985 to 2001 (not shown). Since the distinction between Stage A and B may not be meaningful during the time period that spans the introduction of PSA testing, which may have biased staging, Stage A and B were combined into a group termed "Organ Confined" (Figure 7.2). The large increase in the overall incidence was mostly organ confined cases, where the rate increased from 38.5 per 100,000 in 1985 to 108.8 per 100,000 in 2001. Locally advanced disease was highest in 1991 at 18.7 per 100,000 but decreased to 8.2 per 100,000 by 2001. The incidence of metastasis has declined since 1992 when the rate was highest at 19.4 per 100,000. by 2001, the rate of metastasis had dropped to 13.5 per 100,000.

There has been a large increase in the age-adjusted incidence of moderately differentiated cases over time, as the incidence is over three times higher in 2001 than in 1985 (Figure 7.3). The incidence of well differentiated cases has dropped 50% since 1993-1994, while the incidence of poorly differentiated cases has remained very stable over the entire 17 year period.

Age-specific incidence rates are shown in Figure 7.4. Incidence rates have doubled for men 55-59 (100 per 100,000 in 1985 to 200 per 100,000 in 2001) and 60-64 (200 per 100,000 in 1985 to over 400 per 100,000 in 2001) years of age. For men 65-69, the rate increased from 300 per 100,000 in 1985 to over 800 per 100,000 in 2001. The pattern of increase in the 70-74 year age group was most similar to the overall age-

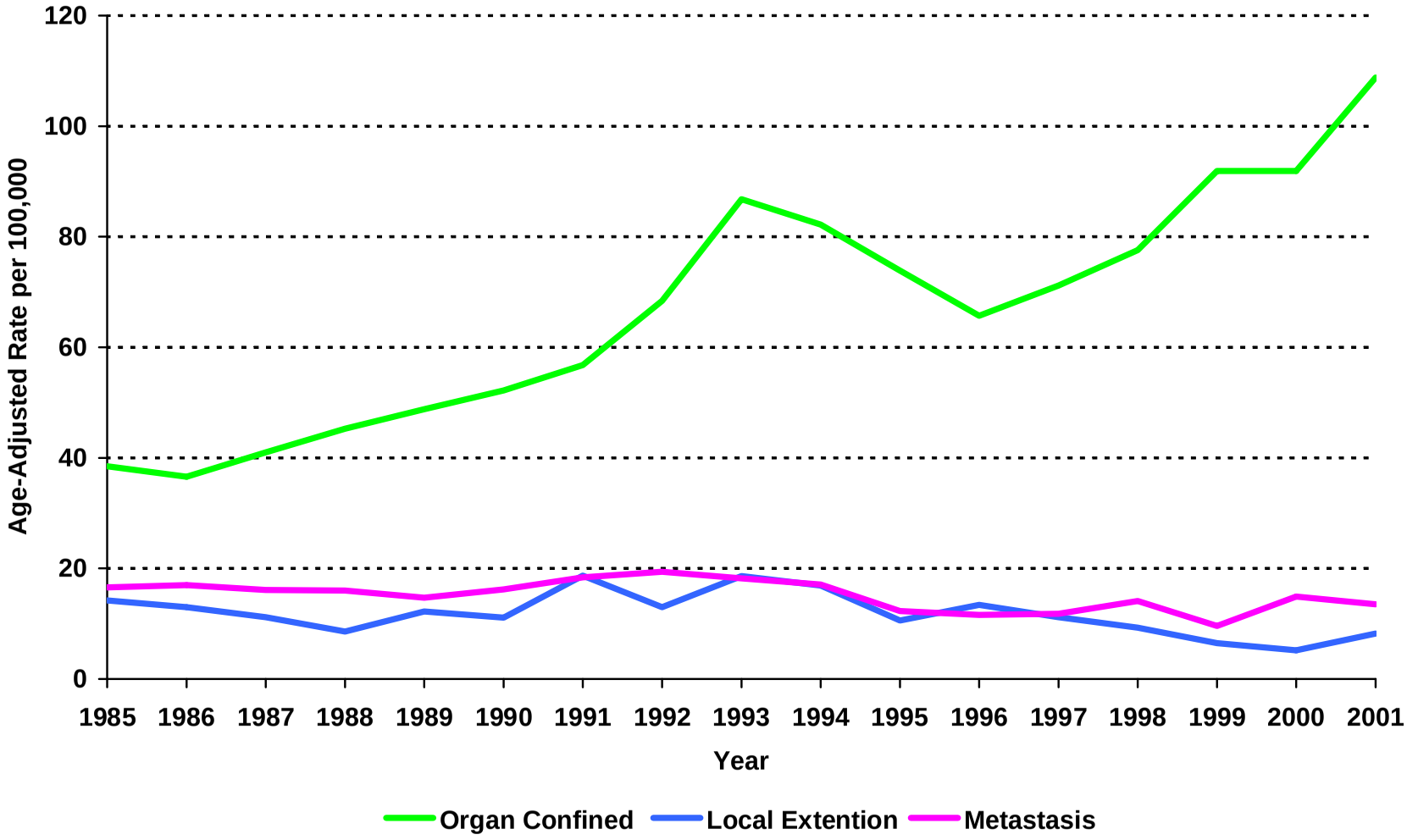

Figure 7.2 Age-Adjusted Incidence Rate for Prostate Cancer in Saskatchewan by Stage at the Time of Diagnosis, 1985-2001

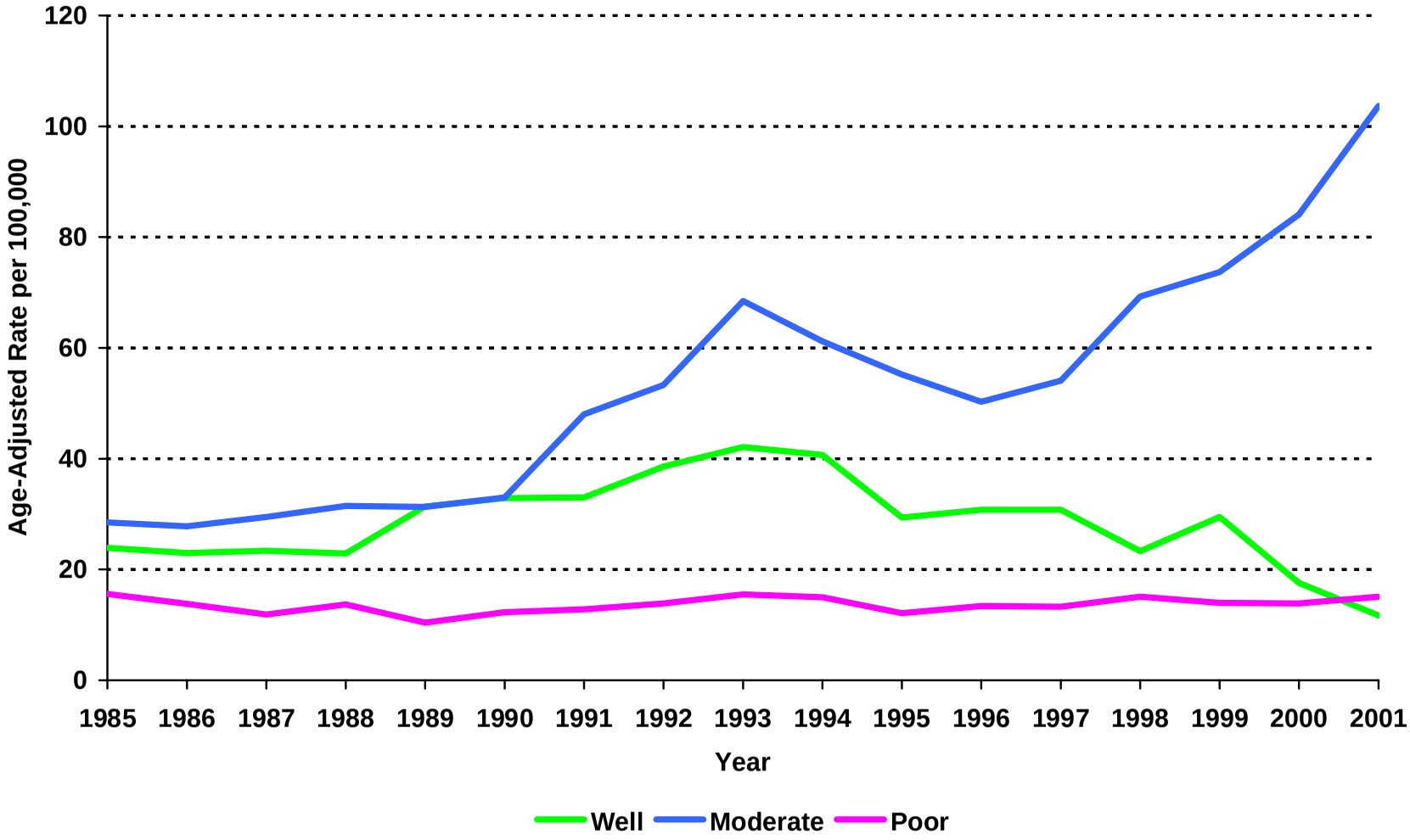

Figure 7.3 Age-Adjusted Incidence Rate of Prostate Cancer in Saskatchewan by Grade at the Time of Diagnosis, 1985-2001

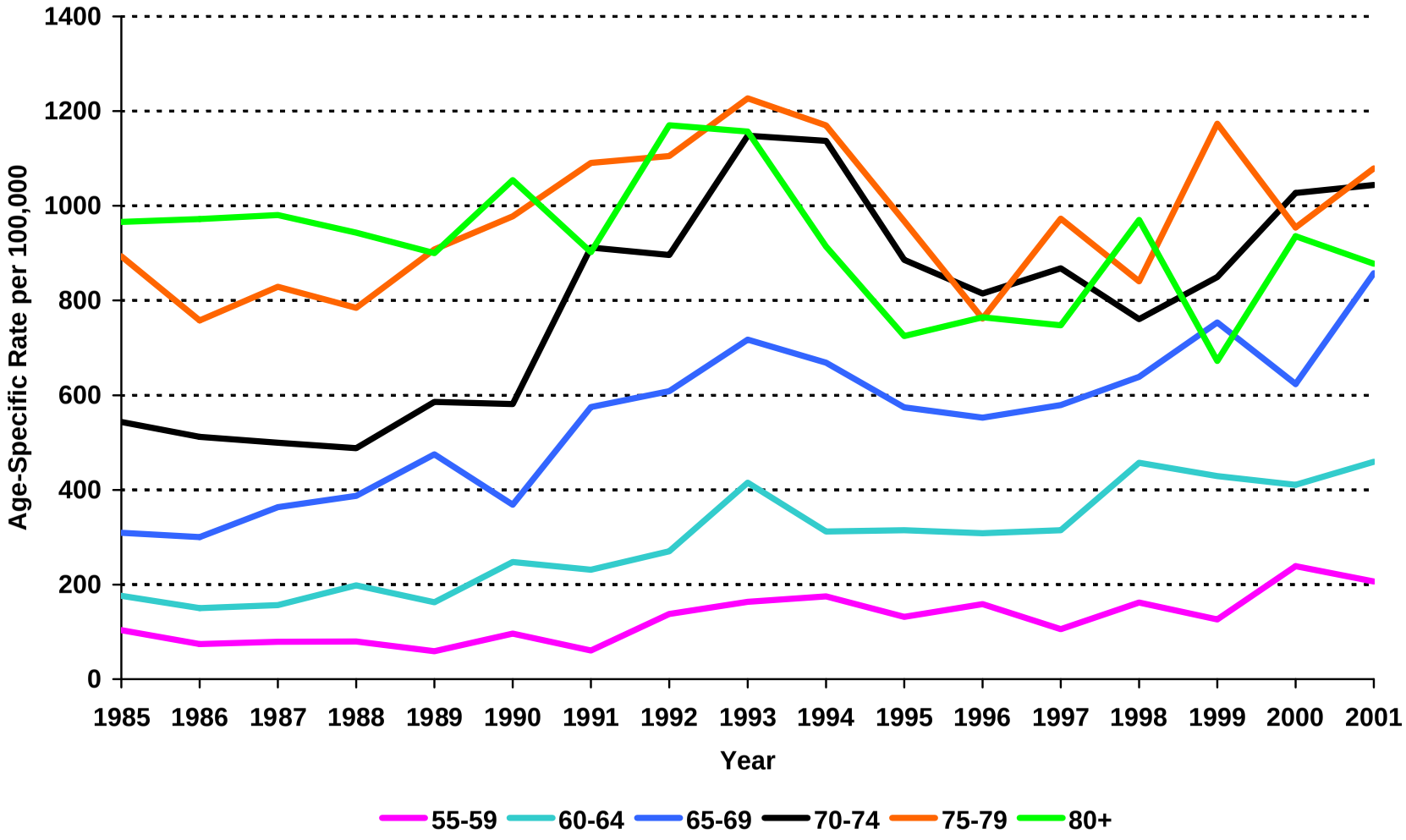

Figure 7.4 Age-Specific Incidence Rate of Prostate Cancer in Saskatchewan, 1985-2001

adjusted rate, with a peak incidence in 1993-1994, followed by decreases to 1998, and another increasing trend to 2001. The pattern was also similar in the 75-79 age group but the change in incidence was not as great as the 70-74 age group. Incidence in the 80+ age group peaked at almost 1,200 per 100,000 in 1992-1993 and has remained below that level ever since. Since 1993, the incidence in the 70-74 and 75-79 year age groups has been consistently higher than the incidence in the 80+ age group.

Figure 7.5 shows the incidence of organ confined disease by ten-year age groups. The incidence has increased by a factor of four for men 50 to 59 years of age, from 13 per 100,000 in 1985 to 51 per 100,000 in 2001. For men 60 to 69, the rate increased from 41 to 135 per 100,000 and for men 70 to 79, the increase was from 84 to 187 per 100,000 for the same years. The organ confined rate did not show any pattern of change for men 80 and older over the 17 years.

The pattern is quite different for the diagnosis of Stage D cases by age as shown in Figure 7.6. For men 70 to 79 and 80+, the average incidence of metastasis from 1985-1989 to 1997-2001 dropped 44% and 39%, respectively. The diagnosis of metastasis in men 50 to 59 dropped from an average of 6.6 per 100,000 in 1985-1989 to 4.8 per 100,000 for 1997-2001, a relative reduction of 27%. For men in their 60's, the average rate fell 21% from 15.8 to 12.5 per 100,000. The diagnosis of locally advanced disease dropped significantly in all age groups, except for men aged 50-59, for whom the rate was stable (not shown).

Age-specific mortality rates from prostate cancer are shown in Figure 7.7. There has been little change in death rates among the 50-59 and 60-69 age groups for the years 1985-2002. When viewed as three six-year periods (1985-1990, 1991-1996, and 1997-2002), the average death rate in the 50-59 year age group was 8.9, 9.9, and 9.1 per 100,000, respectively. In the 60-69 age group, the average death rate for the three periods was 57.2, 66.7, and 56.4 per 100,000, respectively. The pattern was different in the two older age groups. Among those 70-79, the average death rate was 222.3, 228.5, and 240.7 per 100,000, respectively, and in the 80 plus age group the average rates were 623.3, 657.2, and 746.5 per 100,000, respectively.

Among the men diagnosed with Stage A prostate cancer during 1985-1999 and who are known to have died (deaths by August 2002), 19% (211 of 1085) died of prostate

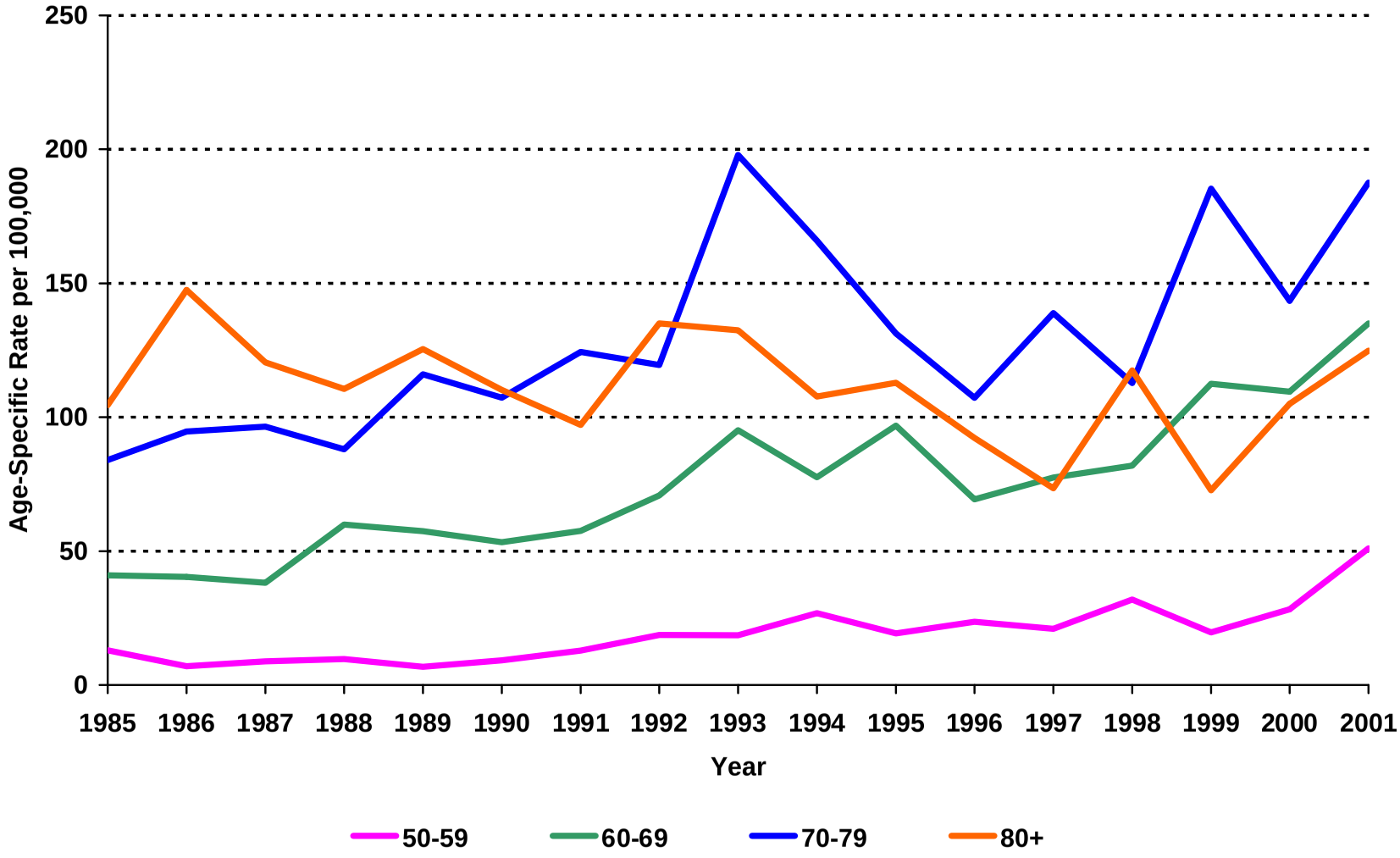

Figure 7.5 Age-Specific Incidence Rate of Organ-Confined Prostate Cancer in Saskatchewan, 1985-2001

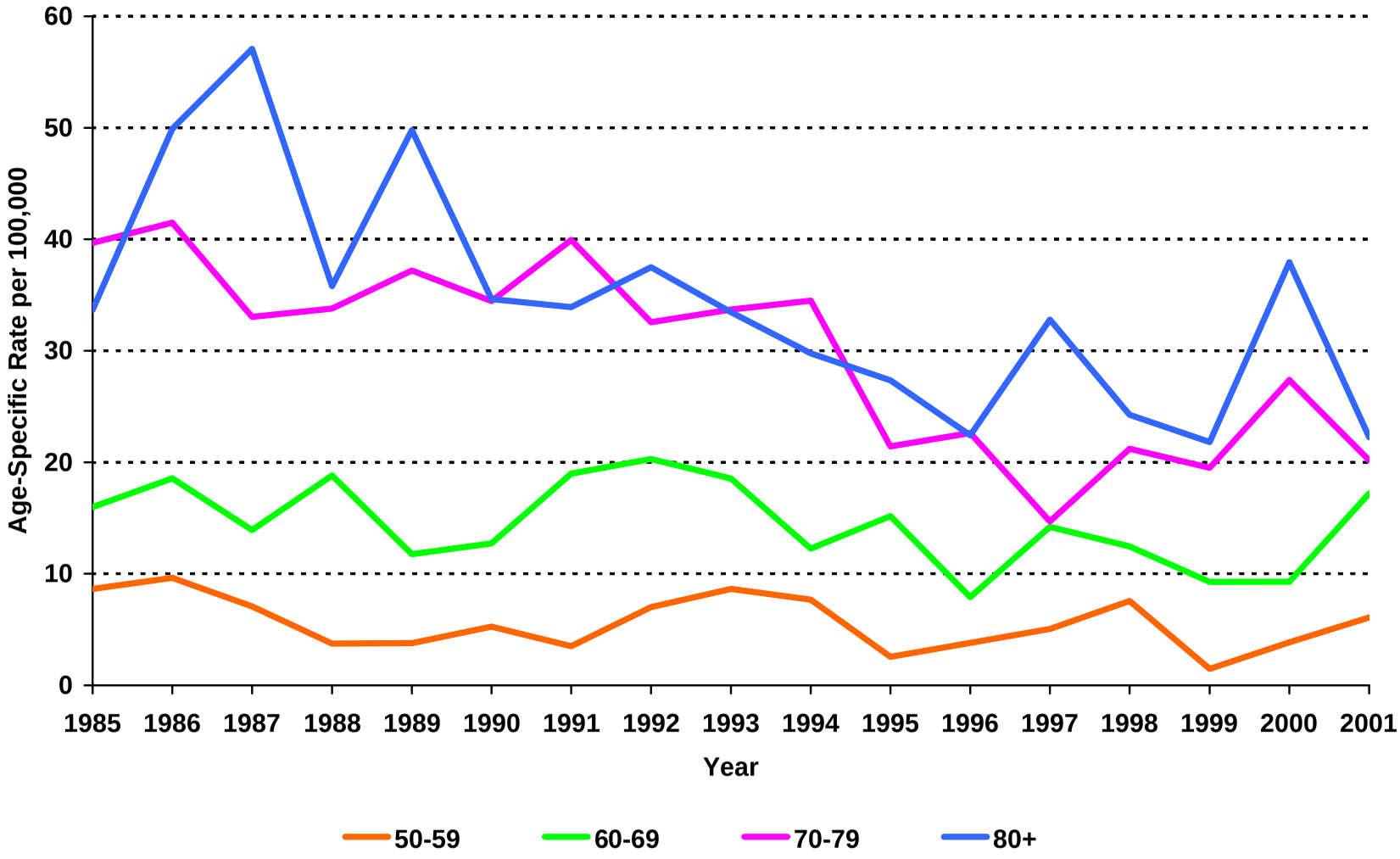

Figure 7.6 Age-Specific Incidence Rate of Metastatic Prostate Cancer in Saskatchewan, 1985-2001

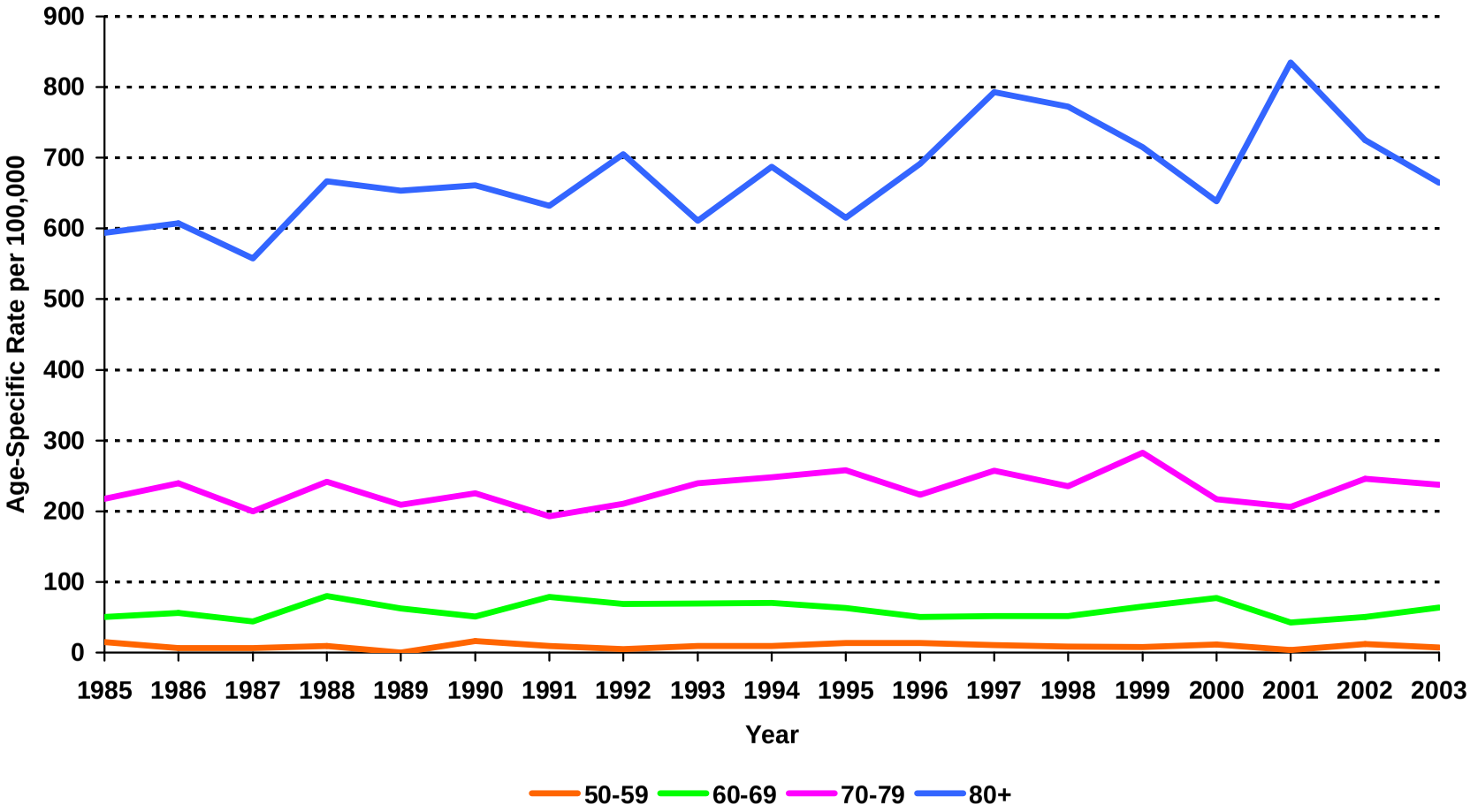

Figure 7.7 Age-Specific Mortality Rate of Prostate Cancer in Saskatchewan, 1985-2001

cancer. Among men with Stage B at diagnosis, 37% (506 of 1367) died of disease, and for men with Stage C, 54.5% (421 of 773) died of prostate cancer. Seventy-eight percent (936 of 1197) of men diagnosed with metastases (Stage D) died of prostate cancer.

The total number of prostate cancer cases doubled over time from 400 to 800. The number of cases with metastasis at diagnosis dropped. For the period 1985-1989, there was an average of 93 Stage D cases diagnosed per year. For the period 1996-2001, the number of Stage D cases dropped 16% to 78 new cases per year. However when viewed as a proportion of total new cases, Stage D dropped from 22.1% of all cases in 1985-1989, to only 11.8% of all new cases diagnosed in 1996-2001, a decrease of 46.7%.

The investigation and management of prostate cancer has changed during the PSA era as well. Table 7.1 shows that prior to the PSA testing (1990) most prostate cancers were detected from transurethral resections of the prostate (TURP) and about one third were diagnosed from needle biopsy. By 2000-2001 however, only about 20 percent of prostate cancers were detected from TURPs and three quarters of cases were diagnosed by needle biopsy. During the same period, the treatment for prostate cancer also changed dramatically. Prior to PSA testing, most cases were treated with radiation therapy, hormone therapy or watchful waiting. Over time, surgery became more common and in 2001 accounted for almost 20 percent of the first course of treatment. Hormone therapy dropped as the first course of treatment from 35.8% of new cases in 1985 to 18% in 2001.

Table 7.1 suggests that men are more likely to have radical treatment during the PSA era. Table 7.2 shows the first course of treatment for men who were 70 or less at diagnosis and who had organ confined disease. These men would have been eligible for all treatment options. Prior to 1990, almost half of men chose radiation therapy and only 14 percent had surgery. For the time period 1997-2001, when PSA was firmly established, 81% of cases had radical therapy, with equal numbers of men choosing surgery as those choosing radiation. The percent of men choosing conservative treatment dropped from 36.8% prior to PSA to 19% in 1997-2001.

7.4 Discussion

Saskatchewan is an interesting population to investigate the impact of PSA testing given the test is available free of charge to all residents, the population is very stable and fairly homogeneous in terms of race. The population is primarily white with a growing

Table 7.1 Method of Diagnosis and First Course of Treatment for Prostate Cancer in Saskatchewan, 1985-2001.

	Method of Diagnosis (% of cases diagnosed that year)			First Course of Treatment (% of cases diagnosed that year)			
Year	Needle Biopsy	TURP	Other*	RP	RT	Hormones	None
1985	34.1	60.4	5.5	2.4	27.9	35.8	33.9
1986	39.5	54.2	6.3	1.5	30.1	35.7	32.7
1987	35.3	57.0	7.6	2.1	29.6	37.7	30.5
1988	35.0	60.1	4.9	5.4	23.4	33.9	37.4
1989	35.3	59.1	5.6	6.0	31.5	31.7	30.7
1990	39.8	54.6	5.5	6.7	27.6	34.5	31.2
1991	51.1	44.3	4.6	8.2	33.6	35.7	22.5
1992	57.5	37.7	4.8	11.1	31.5	31.2	26.2
1993	67.7	27.3	5.0	8.9	30.7	33.0	27.3
1994	74.5	20.9	4.6	10.7	32.6	31.1	25.6
1995	73.8	24.8	1.3	10.1	32.9	30.2	26.8
1996	75.1	24.0	0.9	11.4	34.6	27.9	26.1
1997	77.7	21.0	1.3	11.7	32.2	28.7	27.3
1998	74.2	22.3	3.5	12.5	30.9	25.1	31.6
1999	76.0	22.5	1.4	14.6	32.1	21.7	31.6
2000	73.8	21.8	4.4	17.9	31.0	23.1	28.0
2001	76.1	19.7	4.3	19.7	32.1	18.0	30.2

*** Other diagnostic methods include clinical and radiological**
TURP is a transurethral resection of the prostate
RP is a radical prostatectomy
RT is radiation therapy

Table 7.2 First Course of Treatment Chosen by Men Who Were 70 Years of Age or Less When Diagnosed with Organ Confined Prostate Cancer, by Time Period

	Choice of First Treatment (Percent of Men)		
Time Period of Diagnosis	Radical Prostatectomy	Radiation Therapy	Conservative Treatment*
1985-1989	14.4	48.8	36.8
1990-1996	32.4	45.4	22.2
1997-2001	39.5	41.5	19.0

First course of treatment was treatment in the first six months after diagnosis

*** Includes hormone therapy or watchful waiting**

First Nations (aboriginal people also known as North American Indian) population. The First Nations group represents about 13% of the total population but only about 5% of the population 45 years of age or older.[171]

In Canada routine screening with PSA is not recommended.[17] Incidence patterns and PSA volumes in Saskatchewan however, suggest a large amount of screening is taking place. Our incidence increased dramatically when the PSA test was introduced and by 2001, 80,000 PSA tests were done in the population that had only 122,000 men aged 50 to 79.[172] There was one downward blip in PSA use in 1995, when provincial guidelines were released in Saskatchewan recommending against routine screening for prostate cancer with PSA.[16] After only one year, test use returned to previous trends, likely fueled by both patient demand and strong recommendations supportive of screening from organizations such as the American Cancer Society and the American Urological Association. While some increasing test use would be for follow-up in men with known prostate cancer, a significant portion must have been for screening purposes given these volumes, this population size, and our current incidence levels.

Screening using the PSA test has resulted in significant changes in the diagnosis and management of prostate cancer. As well, tumor and patient characteristics have changed considerably. In the United States, stage migration occurred to more organ confined tumors at diagnosis during the PSA era.[173, 174] Patients are also younger at diagnosis during the PSA era which has resulted in a shift towards more definitive treatments such as radical prostatectomy and brachytherapy, while the proportion of cases treated with external beam radiation and hormone therapy remained fairly stable.[175] In Canada, the age-adjusted rate of radical prostatectomy increased from under 20 per 100,000 in 1990-91 to 71 per 100,000 by 1998-99.[176] In Saskatchewan, we also saw a shift in the age of men diagnosed. Prior to PSA testing, 30% of men were under 70 years of age at diagnosis and by 2001 this had increased to 42%. Consequently, we have seen similar changes in the first course treatment, with 20% of men having definitive surgery in 2001 compared to less than 5% prior to PSA testing.

We used a modified American Urological Association staging system for our chart review. It would have been informative to break down the staging into sub

categories given the numbers of cases we had but this could not be done reliably in a rather large portion of cases in our population-based study.

Whether mortality reductions will result from the earlier diagnosis of prostate cancer and from the shift to more radical (curative) treatment intent is unknown. In a study looking at treatment patterns and mortality in Connecticut, Iowa, and New Mexico, radical prostatectomy was found to have increased by factors of 3-4 since the introduction of PSA testing, similar to what happened in Saskatchewan.[177] In Connecticut and Iowa, mortality was shown to increase but it decreased in New Mexico. In Saskatchewan we found death rates were stable for the younger age groups but increased in the 70-79 and 80+ age groups for the years 1997-2002.

An investigation of incidence and mortality trends in the United States and Canada showed that mortality from prostate cancer in Canada was declining in men over 60 years of age after 1993.[178] Prior to these declines, mortality had been increasing since 1969. Saskatchewan represents only about 3% of the population of Canada therefore the Canadian rates are minimally influenced by the Saskatchewan population. The trends witnessed in Canada are likely partially due to attribution bias, a misclassification of cause of death brought on by changing incidence trends that influence physician's decisions about reporting cause of death on death certificates.[179,180] This bias was likely partially present given the prostate cancer mortality in Canada was increasing up to 1993 then dropped afterwards, which was the same pattern that happened with Canadian incidence rates. This bias could have been more prevalent in Saskatchewan, because PSA use was likely more common here than the rest of Canada as indicated by our overall higher incidence rates and free availability of PSA, which was not common in all provinces. This could explain our slightly higher age-adjusted prostate cancer incidence rates for the years 1994-2002 and subsequently our higher mortality rates.[4]

Prostate cancer tends to be slow growing and the prevalence of latent tumors (those with minimal risk of metastasis) is high in older men.[181] Detection of these latent tumors through increased screening activity would result in unnecessary treatment of men who may not require medical intervention.[174] But PSA testing has primarily resulted in an increase in the diagnosis of organ confined moderately differentiated tumors. This finding is consistent in areas where widespread PSA use has taken place.[173,175,180] These

tumors are considered medically important and are still curable using current techniques.[173,182] The shift towards moderately differentiated tumors is consistent with diminishing low grade detection through the 1990s, as low grade tumors are now more commonly referred to as non invasive atypical adenomatous hyperplasia.[183]

Screening would be expected to reduce the incidence of metastatic disease and eventually lead to reductions in mortality.[164] In Saskatchewan, the reduction in metastasis was only in men in their 70s and over 80, but not in younger men. As well, the increase in organ confined disease was in the younger men and not older, suggesting that PSA testing has shifted the detection of distant disease in older men to diagnosis of earlier organ confined disease in younger men. This might result in a reduction of prostate cancer mortality in the older men but still could have very little influence on their overall survival because of competing risks in old age.[184] What is more noteworthy perhaps, is that the incidence of metastatic disease has not changed in men under 70, the men who have more to gain in overall survival if prostate cancer deaths could be avoided.

The study was population-based and provides a thorough understanding of the affect of PSA testing on tumour characteristics and treatment patterns. It is clear from the data retrieved from the Cancer Registry however, that cases are missing in the 80 and over age group. Given its strong relationship to age, it did not make sense that the age-specific rates of men in their 70 would overtake the rates for men in their 80s. Consultations with urologists in the province indicate that these older men are more often clinically diagnosed and not reported to the Registry even though they should be by legislation. This makes trends for the oldest group very difficult to interpret given the level of under reporting is unknown.

Investigation of tumour and treatment patterns provides useful information about the impact of widespread PSA testing in the population. The limitation is that it does not tell us whether PSA testing is beneficial or not for mortality. In our population we have seen no change in mortality trends. But it could be that not enough time has elapsed for a mortality benefit to materialize. Had our mortality trends shown change, it would still be difficult to attribute any reduction solely to PSA screening given the changes that also occurred in treatment over the same years. Benefit of PSA screening for prostate cancer will only be proven through randomized screening trials.

The European Randomized Screening for Prostate Cancer trial is not expected to have results until the end of 2008.[185] The Prostate, Lung, Colorectal, and Ovary cancer trial will also not have results for a number of years yet.[186] In Saskatchewan, where widespread use of the PSA test has been in place for 18 years, prostate cancer mortality has thus far not declined.

8.0 GENERAL DISCUSSION

There were a number of key objectives associated with this research. One objective of this research was to determine the extent of PSA testing in Saskatchewan, and determine the impact of testing in the population which has had free access to the test since 1990. Another objective was to explore changes in the case mix and clinical management of prostate cancers diagnosed during the time of PSA testing. The findings were striking.

Prostate cancer has been the most common diagnosed cancer in Saskatchewan for many years. During the PSA era there was a dramatic increase in the number of new cases. In Saskatchewan before PSA testing there were some 500 new cases per year, but in the PSA era this number had grown as high as 900. The increase has been seen in all age groups most notably those under 80 years of age. In fact, cancer incidence is now higher in men 75-79 than it is in men over 80, a finding that contradicts what we know about prostate cancer risk continually increasing with age. There are two likely explanations for this. One, more PSA testing occurs in men under 80, so more men are investigated and found to have disease since the prevalent pool is large. Second, it is almost a certainty that many men over 80 are diagnosed with prostate cancer clinically and many of these are not reported to the provincial cancer registry although they are supposed to be by legislation. Regardless, the health care system is treating a significantly higher number of new cases per year than it did prior to PSA testing.

The increase in prostate cancer incidence largely consists of organ confined moderately differentiated cases and this is consistent with screening activity and what has been witnessed in other jurisdictions where PSA testing is common. The diagnosis of metastatic disease is also showing signs of dropping in the population. However, we have not seen any drop in prostate cancer mortality as yet in Saskatchewan. Given that ongoing screening trials have not yet shown mortality benefit from screening for prostate cancer, it is difficult to know whether all the screening activity will result in reductions. It may be that enough time has not yet elapsed for the reduction to have occurred, or it

may be that screening will have no impact whatsoever on mortality. The answer remains unknown.

PSA testing has also significantly changed how prostate cancer is managed. More cases are now diagnosed by needle biopsy (at least 75%) versus transurethral resections of the prostate, which was much more common prior to PSA testing. In other words, where we used to find prostate cancer serendipitously (60% diagnosed by TURP prior to PSA testing), we now find it because we are looking for it. As well, in Saskatchewan we are finding it more commonly in younger men, as the cancer incidence rates more than doubled in men 55-59, 60-64 and 65-69 years from 1990 to 2001. This potentially could prove beneficial, as younger men have more to gain from early diagnosis than men in their 70s who have less life expectancy. Treatment patterns have also changed with the diagnosis of younger men in recent times. More men are being treated with radical surgery (40% of men under 70 years) and fewer men being treated by hormone therapy than prior to PSA testing.

These changes have been largely driven by the use of the PSA test in Saskatchewan. The test has been available for physicians for use at no cost to patients since 1990, a fairly unique situation in the context of practices seen in Canada and abroad. This research shows PSA testing is very common in Saskatchewan with many more men having had at least one PSA test than suggested by previous surveys. The study showed that men of all ages are having PSA tests, many younger than 50. Surprisingly, 27% of men in their 40s were found to have had at least one PSA test in the five-year period of study. As well, over 5300 tests were ordered for men less than 40 years, a result not remotely expected. Even organizations that support PSA testing do not recommend screening in these age groups. Many men over 80 are also tested in Saskatchewan (over 60%), although that could be for various reasons; follow-up of clinically diagnosed prostate cancer, investigation of symptoms etc. Still, these are astounding levels of testing in the absence of proof that prostate cancer screening is beneficial.

PSA test use was found to be all over the map, literally. Geographically, testing rates varied in Saskatchewan, with men in northern regions being tested less frequently. Even excluding the far North, the range varied by 20 percentage points between health

regions in all age groups. Limited access to general practitioners would certainly contribute to variation in these rates since they order about 90% of the PSA tests and in Saskatchewan, we know there are rural and remote areas with shortages of physicians.

PSA testing frequencies among men with no previous prostate cancer diagnosis were also extremely variable, some men having one test in a five-year period, others having 20 or more. Among the youngest men less than 40 years of age with no prostate cancer at the time of their PSA test, 16% of men tested had more than one PSA in the five-year period and in the 40 to 49 year age group, this was 30%. The lack of clear guidelines or perhaps guidelines that are supported by clear evidence creates an environment prone to considerable variation among physicians and how they are using the PSA test. There is without doubt, substantial inappropriate use of the PSA test in Saskatchewan.

As expected, PSA test results in the population were very age-specific and would suggest that referrals to urologists could be better controlled if age-specific levels for further follow-up were used. This research shows the cumulative distribution of total PSA in the population diagnosed with prostate cancer and those who were not. Choosing which cutoff depends on ones perspective of the tradeoff between sensitivity (finding cancer when its there) and specificity (not referring men who do not have cancer). If finding cancer is most important, total PSA will have to be lower in each age group but then many men would need to be referred who do not have cancer.

Biopsy rates however, can likely be reduced and not at the expense of prostate cancer detection by using age-specific cutoffs for further investigation. PSA levels increase with age so it makes sense to have "abnormal" levels that reflect that very strong relationship. As well, the number of urologists in Saskatchewan is low, so anything that streamlines their time and has them investigating more relevant cases would be very beneficial and more efficient.

We experienced an interesting natural experiment in Saskatchewan with the addition of the reflex testing procedure to determine the free-PSA ratio among all men with a total PSA in the 4.0 to 10.0ng/ml range. This *experiment* was population-based and provided an excellent opportunity to analyze the impact of the additional information on men and their outcomes after testing. The impact was found to be age-specific. Men

in their 50s had a statistically significant 53% increase in cancer detection rate while the biopsy rate increased 20%. For men in their 70s, there was a significant 17% reduction in biopsy rate with no change in cancer detection. Overall for men aged 50-79 the reflex process resulted in slightly fewer biopsies (reduction of 4.7%) but overall, better cancer detection (increase in detection rate of 8.7%), a very significant finding in support of reflex testing and the fPSA test.

This research did not investigate the reasons for observed testing levels in Saskatchewan. But there are some factors that certainly play a role. One major driver of PSA use has to be that in Saskatchewan PSA testing is available free of charge to all men. If a man wants the test, he is most likely going to have it since physicians have little time to discuss all the potential benefits and harms; it is easier and quicker to just order the serum sample. The conflicting guidelines and recommendations about prostate cancer screening means that physicians will be on both sides of the argument depending on their own personal beliefs about prostate cancer screening. If physicians are pro prostate cancer screening, they can find recommendations to support that activity, and if they do not support screening, they can find the evidence for that as well. Until the screening trials provide the definitive answers about prostate cancer screening, it will be left to physicians and men to make their own decisions about whether to have a PSA test or not for screening for prostate cancer.

These studies highlight the opportunity that exists in Saskatchewan for further research on PSA testing and prostate cancer. We have an excellent population-based cancer registry, PSA data that resides in only two locations for the province and is in electronic format, and linkage capabilities to other data sources at Saskatchewan Health. The PSA data used in these projects is likely unique in the world in that all PSA records are accessible and we have the ability to determine whether PSA testing was in men with or without known prostate cancer at the time of their test.

Saskatchewan has a Health Information Protection Act which is fairly stringent for conducting such linkage studies. Acquiring data from these sources and linking them is a very time consuming endeavor. In future, it would be beneficial if this data was more readily available so that evaluations and research could be timelier.

9.0 STUDY LIMITATIONS

The study was conducted to investigate the use of PSA testing and impacts on the Saskatchewan population. Screening rates and associated measures such as sensitivity and specificity were estimated in the population. Information about the reason for the PSA test was not available. So while these measures were calculated, they certainly would be affected by more knowledge of risk in the men tested. As it is, the screening rates are really more accurately prevalence rates. The estimates of sensitivity and specificity would certainly be impacted by weeding out the higher risk men (with symptoms or family history of prostate cancer) which would be more common with increasing age. Therefore, the estimates are really measures of the combined impact of all PSA testing for all men in the population, and not strictly speaking the screened group of low risk men.

As well, the "true" disease status of all men in the population is not known. It was possible to eliminate men who were already diagnosed with prostate cancer which was beneficial to estimate screening rates and the associated measures of sensitivity and specificity. But it would be the case that some men in the group labeled "without cancer" would certainly have had prostate cancer. Not every man in the population has a biopsy, even among men with elevated PSAs. So there would be some contamination in the non cancer group with men who had not yet been diagnosed but will be in future. At the same time, this is the reality of the real world situation, where not every man is thoroughly investigated for a host of reasons. So the estimates of sensitivity and specificity are reflective of the real population circumstance.

The study period covered five years at a point when PSA testing had been available in Saskatchewan already for seven years. Some of the study results indicated men who had one PSA test during that period. Given a seven year period prior to the study dates, it is very likely some percentage of these men were in fact not receiving their first PSA test, but rather subsequent ones.

There were also some missing PSA records from this five-year period. In total the data contained about 80% of all PSA tests in the province. Therefore all of the prevalence and screening rates were certainly underestimated, potentially by as much as 20% and more likely in the Saskatoon Health Region. As well, the data covered a time when PSA testing was in fact still on the increase. In the first year of this study, 1997, there were about 50,000 PSA tests reportedly done in Saskatchewan. By the end of the study period, 2001, there were about 80,000 reported. So the prevalence and screening rates reflect this period when the testing volumes were still be increasing. After 2001, it is known that the PSA testing levels became stable in the 80,000 to 90,000 range of tests per year. So for the five-year period of this current study, a total of about 315,000 PSA tests were done, of which 250,000 were retrieved, but the subsequent five years 2002-2006 would have had well over 400,000 tests, a minimum 27% increase from the previous five-year period.

The Saskatchewan Cancer Registry apparently is missing some records for prostate cancer cases diagnosed in men 80 and over. As witnessed, the incidence rate for men in their 70s has over taken the rate for men 80 and over, contrary to what would be expected for a disease that is so age related. Younger men would be more aggressively investigated and as such much more likely to have a biopsy to confirm disease than older men who would have less life expectancy and more co-morbid conditions. This made interpretations of the 80 and over group difficult and as such this group had to be omitted from some analyses.

10.0 STUDY IMPLICATIONS

Limitations aside, the study reveals some striking results that do support the requirement for action and policy or guideline development. In Saskatchewan, we must realize and accept that prostate cancer screening is in fact very common. The question is not whether we should be screening or not, but rather given that we are screening, how do we best control and manage the activity so over testing can be limited? The only solution to preventing use of the PSA test would be for the government to de-insure it, which in all probability is highly unlikely after 18 years of availability, even if the current screening trials reveal little or no benefit. The implication in Saskatchewan is, given we are likely already screening over 80% of men aged 50 to 79, we must better manage use of the PSA test and ensure appropriate follow-up for men with high PSA levels.

Even though information was missing about the reason for the PSA test, the variation in testing patterns by age group, the frequency of testing in men, and the geographic variations indicate physicians are unsure how or when to use this test and what appropriate follow-up should occur. There are many different screening guidelines in existence however, and currently no randomized trial evidence of overall mortality benefit. So we will need to develop an action plan to manage the use of the PSA test that will appropriately fit in the Saskatchewan context.

An action plan will need to include a number of elements. First, information and recommendations about appropriate use of the PSA test based on the most current evidence needs to be developed. This will help ensure that men who do not need a PSA test, for example men under 50 years of age with no symptoms of disease or men over 80, are not screened. As well, recommendations about repeat testing in asymptomatic men would hopefully prevent some men from being tested more often than necessary. Development of recommendations will require thorough investigation of current knowledge and understanding of existing guidelines as they relate to the experience in Saskatchewan.

Secondly, getting this information to the providers will require a significant education component. A communications strategy for these recommendations would need to be developed, to ensure the information gets to providers in the most concise and practical method to improve and maximize uptake. How the information is packaged and provided would be key elements.

Establishing such an action plan for using the PSA test will require a multidisciplinary approach. A steering committee including partners representing general practitioners, urologists, Cancer Agency experts, and the labs involved in PSA analysis would need to be involved so that physicians will be more likely to support the recommendations. Non provider groups might need to be involved as well, such as the Prostate Cancer Support Network, the Cancer Society and the Ministry of Health.

Saskatchewan is in a unique position as well to monitor use of the PSA test at the population level and track practice patterns and outcomes. There is an opportunity to make great contributions to the analysis and impact of population-based PSA screening for prostate cancer, given we are essentially already doing population level screening. The Saskatchewan Cancer Agency has a Prevention Program for Cervical Cancer (PPCC) screening program using PAP testing that could be a model for prostate cancer. In the PPCC, only two labs analyze PAP tests and both labs submit the test results electronically to a central database managed by the Saskatchewan Cancer Agency. A similar approach could be done with PSA tests, housing the data in a central database. This would enable the Agency to track PSA use, follow-up patterns for men tested, evaluate outcomes and become an important information source for physicians about use of the test.

The ongoing screening trials should be publishing results in 2009. Once these have been reported, a decision could be made about the development of an official program for prostate cancer screening. If the population-based database is already in place, it will be easy to incorporate a program with decision rules based on the trial results.

A number of recommendations are suggested.

1) Results of these projects need to be shared with major stakeholders; Saskatchewan Health, the two labs that analyze PSA in Saskatchewan, the Saskatchewan Cancer Agency, and the urologists and general practitioners in the

province. Recommendations should be developed about the use of the PSA test in Saskatchewan. While it is not presently reasonable to assume testing can be prevented since it is so entrenched in our population, we should at least be able to provide recommendations and information to better control who is tested and how often, to eliminate waste and unnecessary use of health system resources.

2) The Saskatchewan Cancer Agency should investigate the possibility of developing a provincial PSA database, with data electronically provided by the labs that analyze PSA samples. An up-to-date population-based database would provide an excellent opportunity for monitoring and evaluation, and would be required in the future should organized screening for prostate cancer be recommended when the ongoing screening trials are completed. The Saskatchewan Cancer Agency has experience in this regard, as it houses all the PAP smear data for the province in a similar fashion, where the labs electronically send PAP test results to a central database maintained by the Agency. Such a PSA database would be unique and provide much more timely analysis and evaluation of PSA use.

11.0 CONCLUSION

Saskatchewan provides an excellent test population to examine the impact of PSA testing on prostate cancer and outcomes due to the unique availability of both the data and the test, which is available free of charge to all men in the population.

PSA testing is extensively practiced in Saskatchewan with over 60% of men 50 to 79 years of age having at least one PSA test between 1997 and 2001. Many tests were done in men under 50 and even under 40 years of age, and many were done in men over 80. Lots of men also had more than one test in the five-year period and this occurred in all age groups, including men less than 40. A majority of PSA tests were ordered by general practitioners but there were also geographic variations in testing prevalence. There is considerable testing in age ranges that simply is not be supported by any evidence whatsoever. Access to GPs and universality of health benefits are drivers of PSA use.

Knowledge of free-PSA level as a percentage of total PSA was found to improve cancer detection while slightly lowering the overall biopsy rate in men 50 to 79 years. We experienced a natural experiment by using the reflex testing process at the Pasqua Hospital lab that applied to the whole population. Reflex testing and knowledge of the fPSA showed better discrimination for biopsy and cancer detection.

Prostate cancer incidence follows the pattern of PSA testing in the population. More testing results in more new cases diagnosed. PSA testing has shifted the diagnosis of prostate cancer to more cases that are organ confined moderately differentiated. Clinical management has changed over time, with most prostate cancer now diagnosed by biopsy and treated with surgery. Although PSA has been around for 18 years, and more favourable cases are diagnosed, no change in mortality has yet been realized.

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13.0 APPENDIX 1

Prostate Specific Antigen (PSA) is found in the blood in three molecular forms: free PSA, PSA complexed with • -1 antichymotrypsin, and PSA complexed with • -2 macroglobulin. Commonly used immunoassays measure total PSA, the sum of the free and complexed forms, but a specialized assay is now available to measure the free form, which is expressed as a ratio of the total PSA.

Recent studies have shown that the measurement of the ratio of free-to-total PSA can improve specificity for distinguishing between benign prostatic hyperplasia (BPH) and prostatic carcinoma. Patients with higher ratios of free PSA are more likely to have benign findings and patient with lower ratios are more likely to have prostatic carcinoma. The following guidelines are utilized for the interpretation of free PSA values in establishing patient-specific risk for prostatic carcinoma:

- Free-to-total PSA ratios of greater than 0.24 are more likely to be benign prostatic hyperplasia. As the ratio increases so does the likelihood of BPH.

- Free-to-total PSA ratios of less than 0.10 are more likely to be prostatic carcinoma. As the ratio decreases, the likelihood of carcinoma increases.

- Free-to-total PSA ratios between 0.10 and 0.24 show substantial overlap of clinical findings with both malignant and benign diagnoses.

- There is some overlap of clinical findings throughout the range of free-to-total PSA ratios. Measurement of free PSA and the resulting ratio is not an absolute test for malignancy.

- The free-to-total PSA ratio is most useful in patients with total PSA values between 4 to 10 • g/L.

All total PSA with a value from 4 to 10 • g/L inclusive will have a free PSA automatically reflexed and the free-to-total PSA ratio reported. Free PSA cannot be ordered as an individual test.

14.0 APPENDIX 2

University of Saskatchewan
Advisory Committee on Ethics in Human Experimentation

May 1, 2001

Certificate of Approval

PRINCIPAL INVESTIGATOR	DEPARTMENT	BMC#
J. Tonita	Saskatchewan Cancer Agency	2001-107

INSTITUTION(S) WHERE RESEARCH WILL BE CARRIED OUT

Allan Blair Cancer Centre
4101 Dewdney Avenue
Regina, SK S4T 7T1

SPONSORING AGENCIES

HSURC application

TITLE:

Impact of Determining the Free PSA Ratio Using Reflex Testing n Saskatchewan

ORIGINAL APPROVAL DATE	CURRENT EXPIRY DATE
May 1, 2001	May 1, 2002

CERTIFICATION

The University Advisory Committee on Ethics in Human Experimentation (UACEHE) has reviewed the above-named research project. The proposal was found to be acceptable on ethical grounds. The principal investigator has the responsibility for any other administrative or regulatory approvals that may pertain to this research project, and for ensuring that the authorized research is carried out according to governing law. This Certificate of Approval is valid for the above time period provided there is no change in experimental procedures.

ONGOING REVIEW REQUIREMENTS

In order to receive annual renewal, a status report must be submitted to the Chair for Committee consideration within one month of the current expiry date each year of the study, and upon its completion. Please refer to the following website for further instructions: http://www.usask.ca/research/ethics.shtml

APPROVED.

D.W. Quest, Chair
University Advisory Committee on
Ethics in Human Experimentation

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